A RANDOMIZED CONTROLLED TRIAL OF INTRAMUSCULAR MAGNESIUM SULPHATE IN NEONATES WITH SEVERE PERINATAL ASPHYXIA

Dissertation submitted to

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

in partial fulfilment of the requirements

for the award of the degree of

D.M. (NEONATOLOGY)

2010 – 2013

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI

CERTIFICATE

This is to certify that the dissertation entitled "**A Randomized Controlled Trial Of Intramuscular Magnesium Sulphate In Neonates With Severe Perinatal Asphyxia**" is a bonafide work done by **Dr.C.N.KAMALARATHNAM** under my guidance and supervision during the period between May 2012 – Feb 2013 towards the partial fulfilment of requirement for the award of **D.M. (Neonatology)** degree examination to be held in August 2013 by the Tamilnadu Dr. M.G.R. Medical University, Chennai.

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DECLARATION

I solemnly declare that this dissertation titled **A Randomized Controlled Trial Of Intramuscular Magnesium Sulphate In Neonates With Severe Perinatal Asphyxia**" was prepared by me in the Department of Neonatology, Institute of child health and hospital for Children, Egmore, Chennai under the guidance and supervision of Prof.J.Kumutha MD., DCH., Professor & Head of the department, Department of Neonatology, ICH, Chennai. This dissertation is submitted to The Tamilnadu Dr.M.G.R Medical University, Chennai in partial fulfilment of the university requirements for the award of the degree of D.M. Neonatology.

Place: Chennai

Date: Dr.C.N.Kamalarathnam

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CERTIFICATE OF APPROVAL

To
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Dear Dr. C.N. Kamalarathnam

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "A randomized controlled trail of intramuscular magnesium sulphate in term infants with severe perinatal asphyxia " No. 08112011

The following members of Ethics Committee were present in the meeting held on 22.11.2011 conducted at Madras Medical College, Chennai -3.

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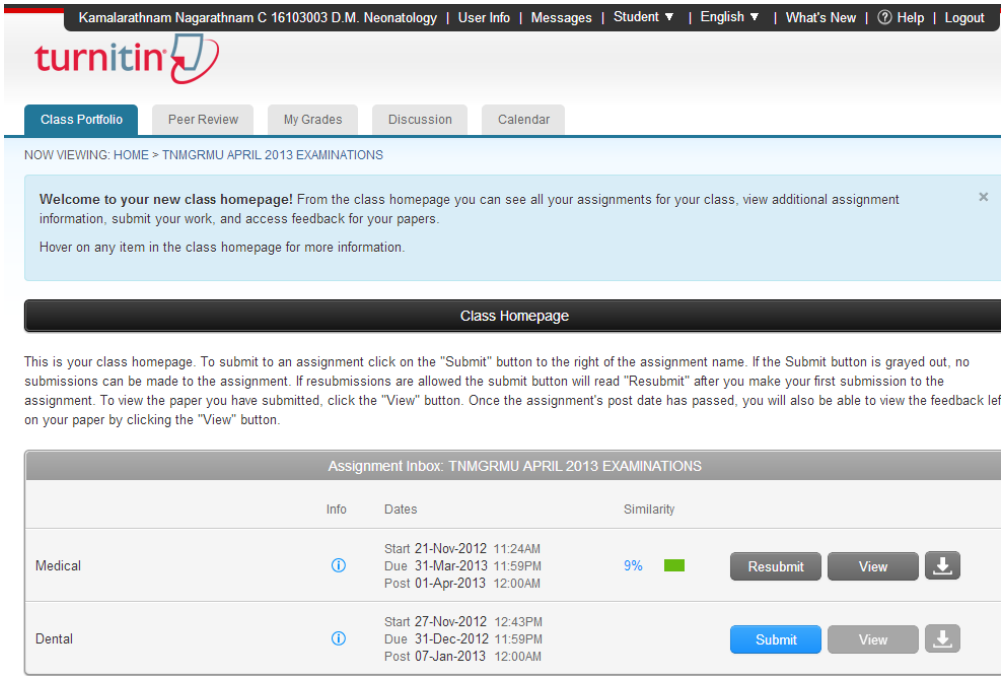
We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee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INTRODUCTION: Neonatal encephalopathy following perinatal hypoxia and ischemia is a major cause of neonatal morbidity and mortality globally. In resource rich countries, the incidence of severe perinatal asphyxia (causing death or severe neurological impairment) is about 1/1000 live births. [1] In developing countries, rates of birth asphyxia are several folds higher, ranging from 4.6 per1000 in Cape Town [7] to 26 per 1000 in Nigeria [8] and fatality rates may be 40% or higher [9]. Data from hospital-based studies suggest an incidence of 5–10/1000 live births [2, 3, 4]. In India, the National Neonatal Perinatal Database reported an incidence of 5% of intramural live births among studies...

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INTRODUCTION

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Neonatal encephalopathy following perinatal hypoxia and ischemia is a major cause of neonatal morbidity and mortality globally. In resource rich countries, the incidence of severe perinatal asphyxia (causing death or severe neurological impairment) is about 1/1000 live births. [1]

In developing countries, rates of birth asphyxia are several folds higher, ranging from 4.6 per1000 in Cape Town [7] to 26 per 1000 in Nigeria [8] and fatality rates may be 40% or higher [9]. Data from hospital-based studies suggest an incidence of 5–10/1000 live births [2, 3, 4]. In India, the National Neonatal Perinatal Database reported an incidence of 5% of intramural live births among studies conducted in 16 medical institutes [5]. As per World Health Organization (WHO) statistics, between four and nine million newborns develop birth asphyxia each year. Of those, an estimated 1.2 million die and at least the same number develop severe consequences, such as epilepsy, cerebral palsy, and developmental delay. [6]

Encephalopathy occurs in 50% to 60% patients with severe perinatal asphyxia [7]. Moderate/severe hypoxic ischemic encephalopathy (HIE) causes significant morbidity and death in the neonatal period and permanent neurodevelopmental handicaps among survivors [8]

Among neonates with moderate HIE, 20% to 37% die and 30% to 40% develop neurodeficits, whereas 50% of patients with severe HIE die and almost all survivors develop neurological deficits [9, 10]. Neurological abnormality at discharge is a strong predictor of long term neurodevelopment delay [11].

Thus perinatal asphyxia and hypoxic encephalopathy is a major cause for neonatal morbidity and mortality. The neurological sequale that follows is a burden to the family & society and there is an urgent need to improve its management. As per WHO, the disability produced by asphyxial injury and its sequelae exceed those due to all childhood conditions preventable by immunization[12].

Primary neuronal injury occurs during the period of hypoxia and ischemia and stops with resuscitative measures. Secondary neuronal injury continues for hours to days even after the reversal of asphyxial event, and excitotoxicity mediated by glutamate is one of the important mechanisms responsible for this type of injury [13]. This secondary phase of neuronal injury may last as long as 72 hours [11, 13, 15,]

During asphyxia there is excessive release and reduced uptake of glutamic acid, predominant excitatory neurotransmitter in brain. Glutamate acts on the N-methyl-D-aspartate (NMDA) receptor, a postsynaptic ion channel in the brain. Increased concentration of glutamate opens up NMDA channels resulting in excessive influx of calcium into neuronal cells leading to neuronal injury [11]

Magnesium is a naturally occurring NMDA receptor antagonist that blocks the influx of calcium at the neuronal ion channel level [14]. Neuronal depolarisation that occurs during asphyxia overcomes this block. Increasing the concentration of magnesium in the extracellular fluid of neuronal cells will restore the block [15].

Thus magnesium can be used to prevent the excitotoxic injury that occurs during the initial hours following the primary neuronal injury. Studies regarding the effects of magnesium after simulated hypoxic-ischemic insults in several animal models revealed beneficial effects in some studies [16,17,18] and no effect in some [19,20]. Some authors have suggested a reduction of cerebral palsy following the use of magnesium sulphate during pregnancy [21, 22] whereas others have not been able to show this [23, 24, 25]. Two prospective human studies have shown improved neurological outcome of term neonates with perinatal asphyxia following IV Magnesium sulphate. (26, 27)

The required serum therapeutic levels of magnesium (1.5 – 2.5 mmols/L) can be achieved with a dose of 250mg/kg given once daily as slow IV bolus infusion [29]. Both IM &IV routes have been recommended in adults in the management of pre eclampsia & eclampsia [30]. Intramuscular Magnesium sulphate is used in neonates for treatment of hypomagnesaemia & tried in the management postnatal apnea [31, 32]. Anticonvulsant effect start almost immediately following IV Magnesium sulphate and is maintained for one hour. Peak action is achieved by one hour and lasts for 3-4 hours following IM Magnesium sulfate [33]. Hypotension & respiratory depression is known to occur with intravenous route and hence close monitoring is required [33].

Intramuscular route of magnesium sulphate has not been tried in neonates with perinatal asphyxia so far. We were able to demonstrate in a pilot study that neuroprotective levels of serum magnesium as

recommended by Levene et al can be achieved with intramuscular injection of magnesium sulphate in term babies with perinatal asphyxia and the levels could be sustained for 72 hours (unpublished data).

With this evidence a prospective double blind randomised placebo controlled trial was planned to determine whether postnatal intramuscular Magnesium sulphate treatment can improve the short term outcome in neonates with moderate to severe perinatal asphyxial encephalopathy.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

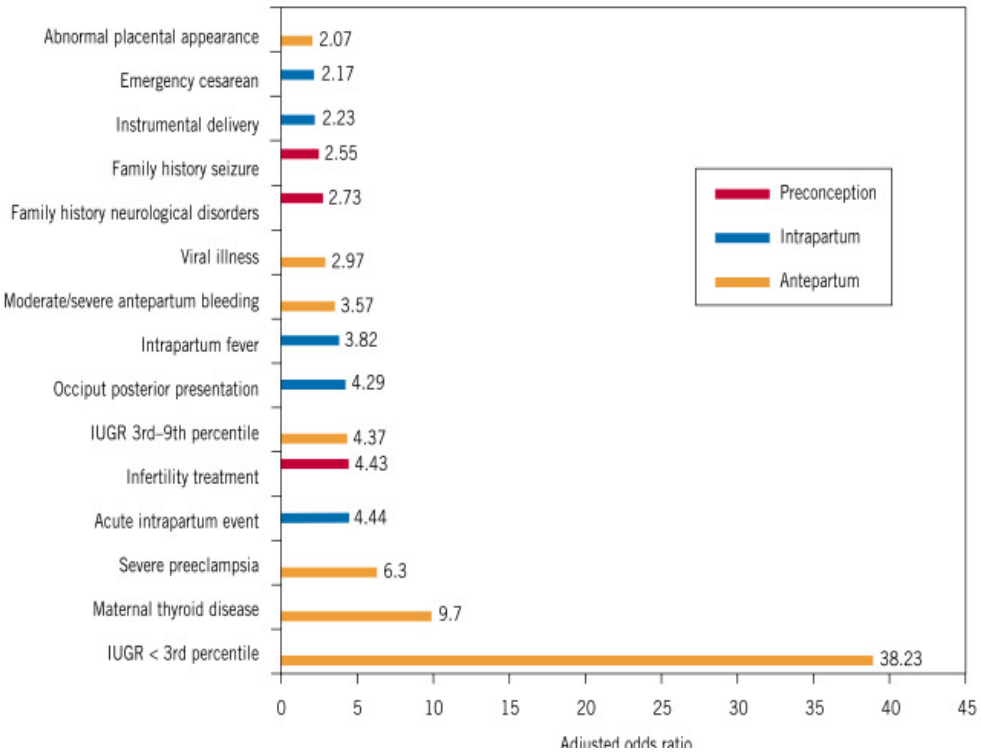
Perinatal asphyxia is an insult to the fetus or neonate due to lack of oxygen and/ or lack of perfusion to various organs. The common factor is deprivation of oxygen to the Central Nervous System. There is a lack of unanimity in the definition of perinatal asphyxia [35]. The World Health Organization (WHO) has defined birth asphyxia as "failure to initiate and sustain breathing at birth"and a score of less than seven at one minute of life, based on Apgar score.

National Neonatal and Perinatal database (NNPD) 2000, has defined moderate perinatal asphyxia as slow gasping breathing or an Apgar score of 4-6 and severe as no breathing or an Apgar score of 0-3 at one minute of life [5]. The essential criteria for for diagnosing perinatal asphyxia as stated by the American college of Obstetricians and Gynecologist and the American Academy of Pediatrics are –

1. Prolonged metabolic or mixed acidemia (pH <7) on an umbilical arterial cord blood sample.
2. Apgar score of 0 to 3 for longer than 5 minutes.
3. Neonatal neurological manifestations eg. seizures, coma or hypotonia, and
4. Evidence of multisystemic organ dysfunction eg. Cardiovascular , gastrointestinal, hematological,pulmonary or renal system in the immediate neonatal period.[34]

Birth asphyxia can be caused by events that occur during the antepartum, intrapartum or postpartum period. Dillenge et al found that asphyxia is primarily antepartum in origin in 50% of cases, intranatal in 40% and postnatal in 10% of cases [35]. In developed

countries with advanced obstetric care, asphyxia is predominantly antenatal in origin or due to intranatal events superimposed on already existing risk factors [4].



Risk factors for newborn encephalopathy

In developing countries studies assessing the timing of insult in an asphyxiated infant are not available. Due to lack of skilled care and higher incidence of complication during delivery intrapartum causes of asphyxia predominate [36].

Ischemia and hypoxia are the two forms of oxygen deprivation during asphyxia, of which ischemia is more important. Cerebral blood

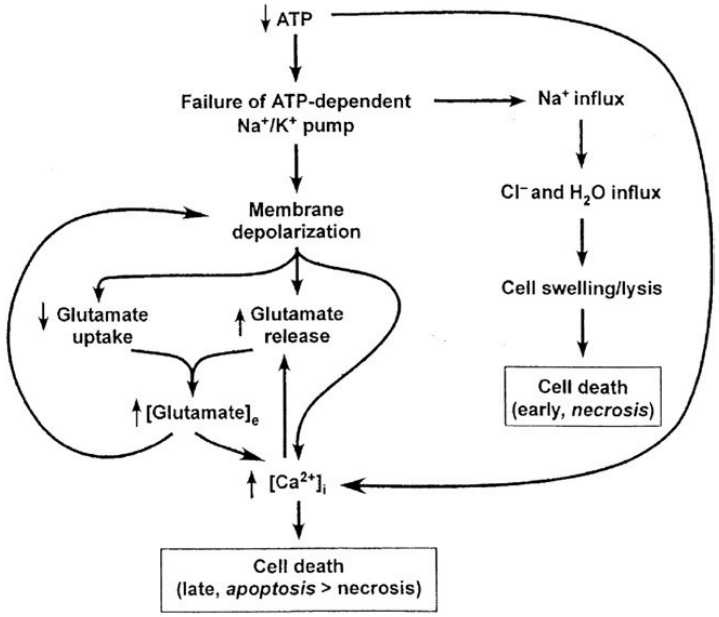
flow (CBF) is maintained at a constant level over a broad range of perfusion pressure.This autoregulation of cerebral blood flow which is operative in both preterm and term infants, results from arteriolar vasoconstriction during increased perfusion pressure and vasodilation during decreased perfusion pressure [6]. Approximate regulatory range is 25 to 50 mmHg mean arterial blood pressure.The size of the range vary with gestational age and post natal age [11].

During moderate to severe asphyxia cerebral vascular autoregulation is impaired and CBF becomes passively related to arterial blood pressure (pressure passive cerebral circulation). The fall in the arterial blood pressure following asphyxial insult leads to decrease in CBF and injury to certain vulnerable brain cells (selective neuronal necrosis).This selective vulnerability of neuronal groups is also due to regional vascular factors and regional metabolic factors. Neuronal injury due to perinatal hypoxia and ischemia is initiated during the insults and extends into the recovery period.

Neuronal injury occurs in two phases. The primary phase occurs during the asphyxial insult and if not corrected leads to a cascade of biochemical events and necrotic cell death. This is primarily due to cellular hypoxia which interrupts oxidative phosphorylation and depletes high energy phosphate reserves.There is a switch to anaerobic respiration and glycolysis becomes the sole source of ATP (an inefficient method of ATP gneneration). This primary energy failure leads to neuronal membrane depolarisation (failure of ATP dependent Sodium Potassium pump) and loss of membrane ionic homeostasis. When ATP level falls below 20% of normal, neuronal injury becomes

irreversible. Synaptic and neuronal conductivity ceases. There is influx of sodium into neuronal cells which is followed by water influx. This leads to cellular edema and necrotic cell death.

Mechanism of neuronal injury in Hpoxic-Ischemic insult



Also there is a cellular efflux of potassium which induces release of glutamate (excitatory neurotransmitter) into synaptic cleft and this coupled with failure of energy dependant reuptake leads to increased accumulation of glutamate in neuronal extracellular fluid. The regional distribution of glutamate receptors, namely N- methyl D-aspartate (NMDA) and alpha amino 3-hydroxy 5-methyl 4-isoxazole propionic acid (AMPA) types, appears to be one of the important determinant of distribution of selective neuronal injury.

Glutamate receptors:

TYPE	Function
Inotropic 1. NMDA receptors 2. AMPA receptors 3. Kainate receptors	 Ca++ entry, Na+ entry Na+ entry, Ca++ entry(in immature neurons Na+ entry
Metabotropic receptors Ibotenate	Mobilizes Ca++ from endoplasmic reticulum

Activation of NMDA receptors by glutamate and increased permeabilty to calcium in AMPA receptors(in immature neurones) leads to increase in cytosolic calcium by enhanced Na + influx which leads to opening up of voltage dependant calcium channels. Sustained membrane depolarisation leads to sustained glutamate release and failure of glutamate uptake.This leads to activation of degradative enzymes like phospholipases A2, Nitric oxide synthase and proteases (Calpain). There is increased generation of free radicals,inhibition of oxidative phosphorylation and direct DNA damage leading to cell death (excitotoxic injury)[7].

During reperfusion and recovery following resuscitation, secondary neuronal damage occurs through large number of known pathways of excititotoxicity leading to mitochondrial failure. This secondary phase of injury occurs slowly (hours to days) and with a normal intracellular pH and stable cardio respiratory status [37]. The cellular response during this phase of neuronal injury is similar to the primary phase leading to a decrease in the high energy phosphate reserves (secondary energy failure).

Reperfusion also attracts monocytes and subsequent inflammation to the site of injury. Additionally reperfusion triggers a cascade of pathologic processes that leads to accumulation of excitotoxic amino acids, increased cytosolic Ca++, generation of free radicals and activation of phospholipases. Increased intracellular calcium activates a cascade of proteolytic enzymes (especially caspases or cystein proteases) leadindg to nuclear fragmentation [38].

Microglial activation after hypoxia-ischemia and reperfusion promotes release of reactive oxygen and nitrogen species as well as cytokines, especially IL-1 and TNF-alpha, which further adds to the neuronal injury [11].

Thus secondary neuronal injury is a consequence of excitotoxicity, inflammation, mitochondrial failure, apoptosis and cytotoxic actions of activated microglia rather than the result of cellular destruction.The severity of secondary energy failure correlates with the severity of seizures and adverse neurological outcome [39].

The clinical features of Hypoxic Ishchemic Encephalopathy (HIE) can range from subtle findings like hyper alert state with mild hypertonia to severe manifestations like stupor, coma and profound hypotonia and absent deep tendon reflexes. Sarnat HB and Sarnat MS had devised a three stage grading system of mild (stage 1), moderate (stage 2) and severe (stage 3) based on clinical symtoms and EEG evaluation [40] .The severity of clinical encephalopathy correlates strongly with neurodevelopmental outcome [41].

Postnatal management of depressed infants begins in the delivery room by following the latest Neonatal Resuscitation Programme guidelines [42]. Supportive therapy along with close monitoring and treament of complications forms the mainstay of management of neonatal HIE.

Neuroprotective therapies are aimed to ameliorate the secondary neuronal injury which progresses for about 72hours after primary neuronal injury. Therapeutic hypothermia (whole body or head cooling) with supportive care significantly improves the neurologic outcome in full-term infants with moderate to severe encephalopathy [43, 44, 45, 46].

The other potential neuroprotective therapies are grouped as follows

1) Agents that inhibit glutamate release (Excitatory aminoacid antagonist)
   - By blocking of presynaptic voltage dependant sodium channels, eg. Phenobarbitone [47].
   - By activating presynaptic adenosine (A1) receptors [48].
   - By blockade of synaptic transmission or blockade of post synaptic glutamate receptors, eg. Magnesium.
2) Blockade of free radical generation or free radical scavengers eg.Allupurinol, desferroxamine, nitric oxide synthase inhibitors [49]
3) Calcium channel blockers: Inhibition of cytosolic calcium accumulation by blocking the entry routes of calcium from the extracellular compartment or from intracellular stores.

Flunarizine has been shown to reduce the extent of hypoxic-ischemic damage in experimental animal models [50].

4) Aminoacid derivatives: HIE disrupts mitochondrial funcution. Acyl CoA molecules accumulate during ischemia and inhibit multiple enzymes. This blocks multiple biochemical cycles like citric acid and urea cycle, glycolysis, gluconeogenisis and catobolism of proteins & fat. Exogenous aminoacid derivative like carnitine facilates transport of acyl moieties across mitochondrial membranes and thus removes the potentially toxic acyl CoA moieties. L carnitine has been shown to significantly reduce the severity of neuronal injury in newborn rats [51]
5) Erythropoetin has been shown to faciltate recovery of sensory motor function following hypoxic ischemic insult in neonatal rats [52]
6) Opioids have been found to be neuroprotective. Retrospective review of neonates who had suffered hypoxic ischemic insult showed that those who were treated with opioid drugs had less brain injury[53].

Among the available glutamate receptor blockers those that act on NMDA and AMPA receptors have received maximal attention, eg. Dextromethorphan, Ketamine, Dizocilpine and Magnesium. Magnesium blocks glutamate receptors within the calcium ion channels. Magnesium, NMDA receptor antagonist inhibits glutamate mediated excitotoxicity and prevents neuronal influx of Ca++. In experimental animal models after simulated hypoxic insults, Magnesium was found to be beneficial in limiting the neuronal damage in some studies.

Spandou E et al found that magnesium sulphate administration resulted in significant protection against moderate hypoxic ischemic brain damage, in seven-day old rats that underwent unilateral carotid artery ligation followed by 1 or 2 hours of hypoxia (8% O_2) [17] .

Mami AG et al studied the effect of magnesium sulphate administration to newborn piglets subjected to severe hypoxia and those with normoxia.The results showed that magnesium sulphate administration prior to hypoxia prevents hypoxia induced increase in intranuclear calcium and IP3 receptor modification and concluded that Magnesium administration prevents hypoxia-induced modification of neuronal nuclear membrane function that leads to intranuclear Calcium dependent transcription of apoptotic proteins leading to hypoxic neuronal programmed cell death[54].

Cetinkaya M et al studied the neuroprotective effect of magnesium on the brain infarct volume in neonatal hypoxic rat model.The percent of infarcted brain volume was significantly reduced in pups who received magnesium compared to those who received saline thus highlighting the possible beneficial effect of magnesium in hypoxic encephalopathy [18, 20].

Greenwood K et al and Penrice J et al did not document any beneficial effect following Magnesium sulphate administration in newborn piglets subjected to hypoxic ischemic insult [19, 20] .

In human studies, mothers exposed to antenatal Magnesium sulphate therapy for eclampsia and for mangement of preterm labour showed decreased risk of germinal matrix or intraventricular haemorrhage in their Very Low Birth Weight (VLBW) babies. [55]

Schendel DE et al studied the relationship between prenatal magnesium sulphate exposure and risk of Cerebral palsy (CP) or mental retardation (MR) among VLBW neonates. It was a cohort study with a follow up upto one year and a subset of cohort followed for five years. The study population was VLBW infants delivered over a period of two years and those among them who survived till infancy. The outcomes measured were

1) Infant mortality among the VLBW infants as determined by the vital statistics record.
2) Development of CP or MR in those who survived for three to five years from the Developmental Disability Surveillance programme.

Among the VLBW infants followed there was no association between prenatal magnesium sulphate exposure and infant mortality, the adjusted Odds Ratio (OR) being 1.02, 95% Confidence Interval (CI) 0.83 to 1.25.

Among the survivors who were followed till 3 to 5 yrs there was a lower prevalance of CP/MR in those exposed to prenatal magnesium sulphate (0.9% in those exposed to magnesium and 7.7 % in those not exposed.Crude OR- 0.11, 95% [CI 0.02 to 0.81] for CP)[21].

Nelson K et al analysed singleton infants who weighed less than 1500gms at birth and had developed moderate to severe cerebal palsy at three years of age. He compared them with randomly selected control survivors (with out cerebral palsy) with respect to whether their mothers had received antenatal magnesium sulphate for any reason. Among mothers whose infants had developed cerebral

Palsy 7.1% were exposed to antenatal magnesium as against 36 % of mothers whose infants did not develop cerebral palsy (OR: 0.14, [95% CI: 0.05-0.51]) suggesting a protective effect of magnesium against CP in VLBW babies [22].

Rouse DJ et al in their randomised placebo controlled double blind multicentric trial of maternal magnesium sulphate therapy for the prevention of cerebral palsy found moderate or severe cerebral palsy occurred significantly less frequently in mothers who had received i.v magnesium sulphate than in those who did not (1.9% vs. 3.5%; relative risk, 0.55[95% CI, 0.32 to 0.95]) . The risk of death did not differ significantly between both the groups. This study also suggests that fetal exposure to magnesium sulfate before anticipated early preterm delivery reduced the rate of cerebral palsy among survivors [56].

Grether et al evaluated the association between intrauterine exposure to magnesium sulphate and neonatal death. They found that magnesium sulphate tocolysis was not associated with increased neonatal mortality in premature infants. Thus selective mortality of vulnerable infants was not the cause for any association of magnesium with reduced long term neurologic morbidity [23].

Ichiba et al in their multicentric randomized controlled trial of iv injection magnesium sulphate in term neonates with moderate to severe asphyxial encepahlopathy found that there was a significant short term neurologic benefit among the neonates who received iv magnesium (250 mg/kg) once a day for 3days. Survival with normal results of cranial computed tomography, electroencephalography and establishment of oral feeding by 14 days of age, was significantly

more frequent in the treated group than in the control group (12/17 vs 5/16, P = 0.04)[26].

The same group of authors tested the neuro protective effect and the safety of injection magnesium sulphate given as i.v infusion along with dopamine infusion to neonates with severe perinatal asphyxial encepahalopathy. They found that postnatal infusion of magnesium sulphate with dopamine caused no change in physiological variables. Deaths and neurological sequelae at 18 months were less frequent than in reported cases(historical control) with the same grade of severity of HIE, and suggested that this treatment may improve neurodevelopmental outcome in infants with severe birth asphyxia[27].

In a recent double blind randomized controlled trial, Bhat MA et al showed that postnatal magnesium sulphate infusion within six hours of life in term neonates with severe perinatal asphyxia is effective in improving the short term neurologic outcomes. Neurologic abnormalities at discharge were significantly less in the treatment group (4 of 18) when compared to placebo group (10 of 18). [OR: 0.22, 95% CI: 0.05-0.9]. There was no significant difference in the in the number of infants initiated on direct breast feeds by seven days of hospitalisation, results of computerized tomography of brain on day 14 of life and the EEG changes between the treatment and placebo group. However a composite measure of no neurological abnormality, normal neuroimaging, normal EEG finding and oral feeding by sucking at discharge was present in 77% of neonates (14 of 18) in the treatment group and 37 % (7 of 18) in the placebo group. (OR: 5.5, [95% CI: 1.2-23.6] P<.02)[28].

Perinatal asphyxia and neonatal encepalopathy is more common in developing countries. Suboptimal intrapartum monitoring further increases the risk of asphyxial encephalopathy in level-1 and level-2 settings (Domiciliary delivery & delivery at Primary health centers) [36]. Availabilty of skilled personnel and optimal monitoring is mandatory for early initiation of i.v magnesium sulphate infusion in neonates with moderate to severe perinatal asphyxia. In this context Intramuscular injection (IM) of magnesium sulphate would be an effective alternate route.

Injection magnesium sulphate is used in neonates to treat neonatal hypomagnesemia and refractory neonatal hypocalcemia[57]. It can be administered both by Intramuscular (IM) and intravenous route (IV). In adults the therapeutic levels of serum magmesium (1.8-1.3 mmol/l) are achieved by both i.v and IM route. [30]. Following IV magnesium sulphate the onset of action is almost immediate and maintained for 30 minutes. The onset of anticonvulsant action takes about one hour following intramuscular route and is maintained for three to four hours [58].

The required neuroprotective levels as recommended by Levene et al is 1.5- 2.5 mmol/L[29]. There are very few studies available in neonates to demonstrate that IM magnesium achieves therapeutic levels of serum magnesium[31,32].

A pilot study was conducted in our neonatal intensive care unit which showed that neuroprotective levels of serum magnesium were achieved and maintained for 72 hours following three doses of 250 mg/kg/day of IM magsulf in neonates with asphyxial encephalopathy.

Adverse effects like hypotension, shock & respiratory depression were not of significant concern during therapy [Unpublished data].

Term babies (≥37wks), born with severe perinatal asphyxia and less than six hrs of age at the time of admission were given three doses of 0.5 mL/kg per dose of 50% Inj. Magsulf (250mg/kg/dose) deep IM, in 2 equal halves, in each thigh. Serum magnesium levels were estimated at recruitment (0 hours), 2, 24, 26, 48, and 50 and at 72hours after the first injection. An average rise of 1.24mmol/L in the mean serum magnesium levels from the base line value follwing each IM injection of magnesium sulphate was documented ($P < .001$) and this was sustained for 24 hours after the third injection.

This paved the way to conduct a prospective randomized placebo controlled trial to determine if IM magnesium sulphate administered within six hours after birth improves the short term outcome (death or survival with neurological impairment) in neonates with severe perinatal asphyxia.

Hypothesis :

Magnesium a naturally occurring NMDA receptor blocker acts as a neuroprotective agent by reducing secondary neuronal injury in moderate to severe asphyxia encephalopathy.

Justification :

Intravenous magnesium sulphate has been shown to be neuroprotective in neonatal asphyxia injury by few authors. It probably reduces secondary neuronal injury through its NMDA receptor blockade effect. Intramuscular Magnesium may be an effective alternative for resource poor settings where the incidence of perinatal asphyxia is high and facility for intravenous infusion may not be always available.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

Aim of the Study

To determine whether intramuscular magnesium sulphate given within six hours after birth improves the short-term outcome in neonates with severe Perinatal Asphyxia.

Objectives of the study:

Primary Objective: Death or survival with neurological impairment

Secondary Objectives:

1) Serum. Magnesium levels
2) Progression of severity of encephalopathy
3) Need for assisted ventilation
4) Incidence of seizures
5) Hypotension requiring inotropic support
6) Time taken for achieving full oral feeds
7) Abnormal findings in neurosonogram done before discharge

MATERIALS AND METHODS

MATERIALS & METHODS

Setting: Tertiary care Maternity hospital with around 15,000 deliveries per year (Inborn unit) and Tertiary care 500 bedded Paediatric hospital (Out born unit) in Chennai, Tamilnadu.

Subjects: Population consisting of all neonates ≥36 weeks, born either vaginally or through caesarean section.

Sample size:

Based on previous Indian studies with an alpha error of 5% and power of 80%, 116 neonates (58 in each group) with moderate to severe asphyxia were studied to allow a detection of 25% reduction in the primary outcome.

Inclusion Criteria:

Babies (≥36wks), less than six hrs of age at the time of admission and born with severe perinatal asphyxia were eligible for the study.

Definition of perinatal asphyxia - babies with any **2** of following **3** criteria

i) H/O fetal distress (late deceleration, fetal bradycardia, meconium stained amniotic fluid).
ii) Need for assisted ventilation initiated at birth & continued for more than two minutes after delivery.
iii) Apgar score of 0 to 3 at 1minute of age.

Neonates were candidates for the study when moderate to severe encephalopathy or seizures were present within six hours of life.

Moderate to severe HIE was diagnosed in these neonates when more than one sign was present in 3 of the following 6 categories.

Criteria for defining moderate to severe encephalopathy

Category	Hypoxic Ischemic Encephalopathy	
	Moderate	Severe
Level of consciousness	Lethargic	Stupor/ coma
Spontaneous activity	Decreased	No activity
Posture	Distal flexion or complete extension	Decerebrate state
Tone	Hypotonia-focal/general	Flaccid
Primitive reflexes		
Suck	Weak	Absent
Moro	Incomplete	Absent
Autonomic system.		
Pupils	Constricted	Deviated , dilated or nonreactive to light
Heart rate	Bradycardia	Variable
respiration	Periodic breathing	Apnea

Exclusion criteria:

No features of HIE by six hours of age.

Major congenital anomalies requiring surgery,

Suspected inborn error of metabolism,

Chromosomal anomalies / syndromes associated with cerebral dysgenesis

Design: Doubled blind randomized controlled trial.

Study period: May 2012 to February 2013

A written consent was obtained from the parents / care givers of the neonate, for willingness for enrolment in the study, after explaining to them about the study.

Randomisation: Randomisation was done through computer generated random numbers placed in opaque envelops. Eligible neonates were randomised into Group-1 (study group) and Group-2 (placebo group). The computer generated code for the intervention drug was available with the Guide and Co-Guide only.

Intervention:

Group I received 3 doses (0.5 ml/kg per dose) of 50% Inj. Magnesium sulphate as IM, 24 hours apart given as 2 equal halves deep IM on each thigh (250mg/kg/dose). **Group II** received 3 doses of 0.5ml/kg per dose of Placebo (normal saline) as IM, 24 hrs apart given as 2 equal halves deep IM on each thigh.

Infants in both the groups were nursed on servo-controlled, open-care beds, with skin temperature maintained at 36.5°C. On day 1 of life, 10% dextrose solution was administered as the maintenance intravenous fluid; electrolytes were added from day 3 of life. Full maintenance fluids were administered initially. If syndrome of inappropriate antidiuretic hormone secretion was proved, fluids were restricted. Depending on the condition of the infant, respiratory support in the form of oxygen therapy or mechanical ventilation and pressor support in the form of dopamine or dobutamine infusion was provided as per standard unit protocol. During the initial 72 hours of life, heart rate, respiratory rate, and oxygen saturation were monitored continuously. Blood pressure was monitored every 15 minutes during the first hour and hourly for subsequent 6 hours through non invasive blood pressure monitoring. After 6 hours blood pressure was monitored every 4 hours.

Assessment of parameters:

The following clinical assessments were made after enrolment**.**

- Assessments of the neurological status at admission, during the stay & at discharge,
- Progression of HIE,
- The type of respiratory support needed,
- Requirement of inotropic support
- Presence of seizures,
- Time taken for establishment of full oral feeds (paladai / breast feeding)

- Neurological examination was performed in the Department of Child Development Clinic in our Hospital at the end of two weeks or at discharge whichever was earlier.

The principle investigator, day to day care givers and the person carrying out the neurologic examination were blinded regarding the drug given to the neonate.

Normal Saline and inj. Magnesium sulphate were packed in similar shaped transparent glass ampules containing 2ml of the respective drugs. They were made to look similar by masking after removing the lables. This made it difficult to differentiate one from the other.

A Certifcate of Analysis was obtained from approved laboratory for both. Normal saline and Inj. Magnesium sulphate, regarding pH, particulate matter, composition as per label claim and test for sterility. Both the drugs fulfilled the prescribed standards of USP, with respect to the tests carried out [annexure-2].

Outcome:

The following outcomes were analysed

Primary outcome: Death or survival with neurologic impairment.

Secondary Outcomes:

- Sr. Magnesium levels in IM & placebo Group. Serum magnesium was analysed by Calmagite method[59].
- Hypoxic ischemic encephalopathy, its severity & its progression
- Need for assisted ventilation

- Seizures requiring anticonvulsants
- Hypotension requiring inotropic support.
- Time taken for attaining full oral feeds (paladai / direct breast feeds)
- Abnormalities in imaging studies

  Ultra sound cranium findings once before discharge or at follow up.

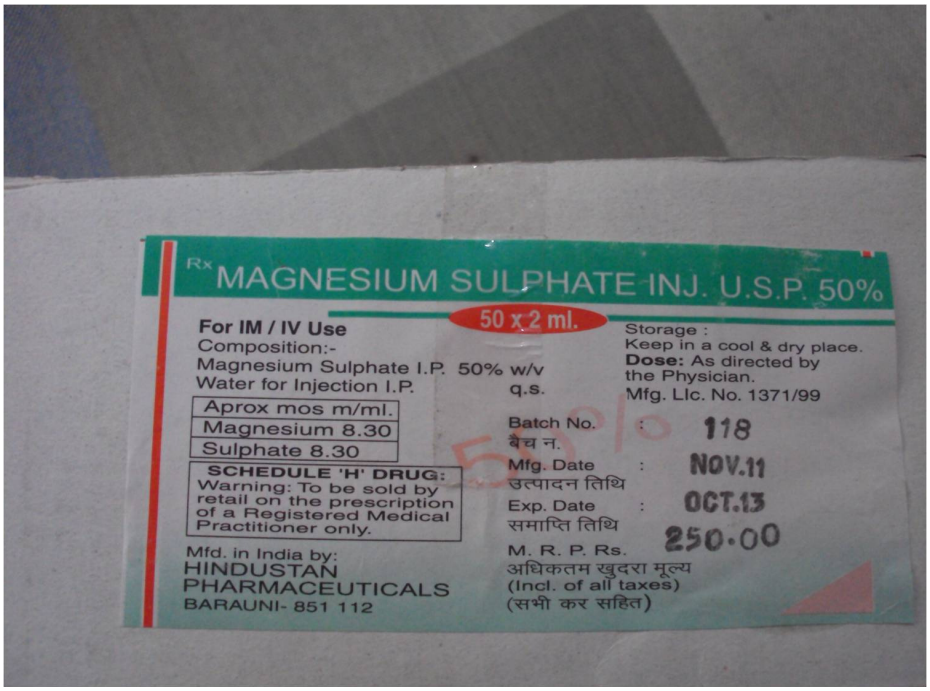
  Abnormal brain CT findings whenever necessary.

STATISTICAL ANALYSIS

All analysis was performed according to intention to treat principle. Standard statistical tests were employed. Normality of the data was analysed using Kolmogorov smirnov test. Categorical variables were analysed with chi square test and continuous variables were analysed using student's independent t test. Association between clinical variables and groups were assessed using chi square test. For significant variables, univariate Odds Ratio with 95% Confidence interval were given. P value of <0.05 was taken as significant. All statistical tests were two tailed tests.

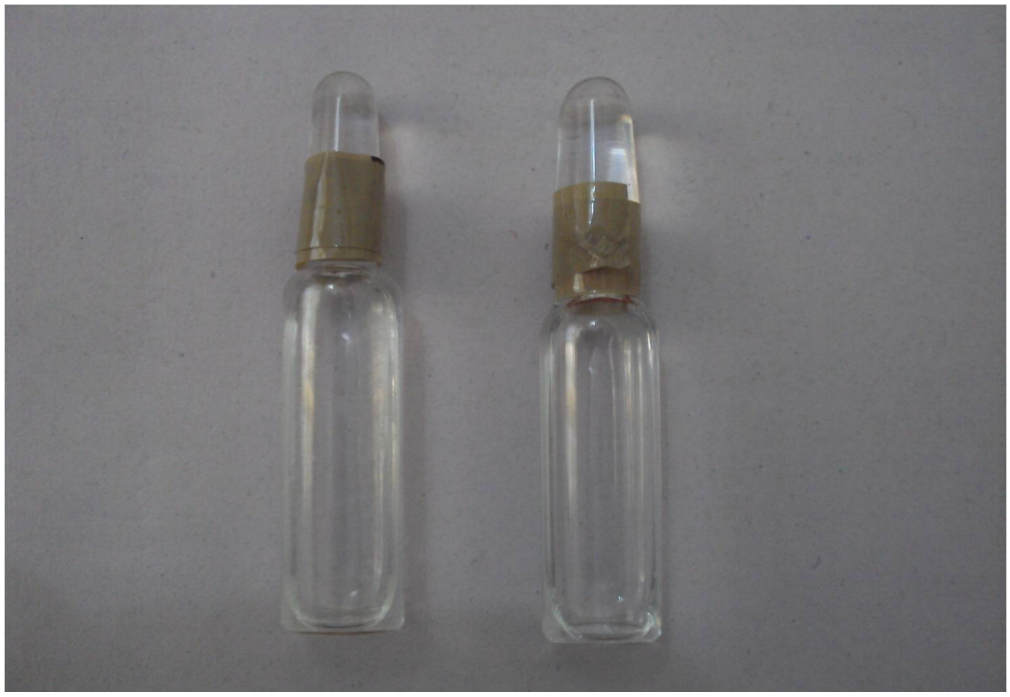
The study was approved by the institutional Ethical committee, No. 08112011.

Injection magnesium sulphate 50% (2ml)



Inj. Normal Saline & Inj Magnesium sulphate before masking

Inj. Normal Saline & Inj Magnesium sulphate after masking



Inj. Normal Saline & Inj Magnesium sulphate masked & packed

RESULTS AND ANALYSIS

RESULTS

A total of 1615 neonates admitted to both outborn and inborn unit of our hospital over a period of ten months were screened for perinatal asphyxia. Three hundred and ninety neonates were diagnosed to have perinatal asphyxia. One hundred and fifty two babies had moderate to severe asphyxia and of these 32 were excluded (23 did not develop features of encephalopathy within six hours of age, seven had major congenital malformation or suspicion of inborn error of metabolism and parents refused consent for enrollment for two neonates).

One hundred and twenty neonates who fulfilled the inclusion criteria were enrolled in the study. Sixty neonates were assigned randomly to saline (placebo group) and 60 to the magnesium group (treatment group). After randomization two parents chose to withdraw from the study even before commencing treatment. Fifty eight neonates in each group continued treatment and were analysed. The baseline maternal and neonatal characteristics are shown in Table – 1 & 2.

Randomization Flow Chart

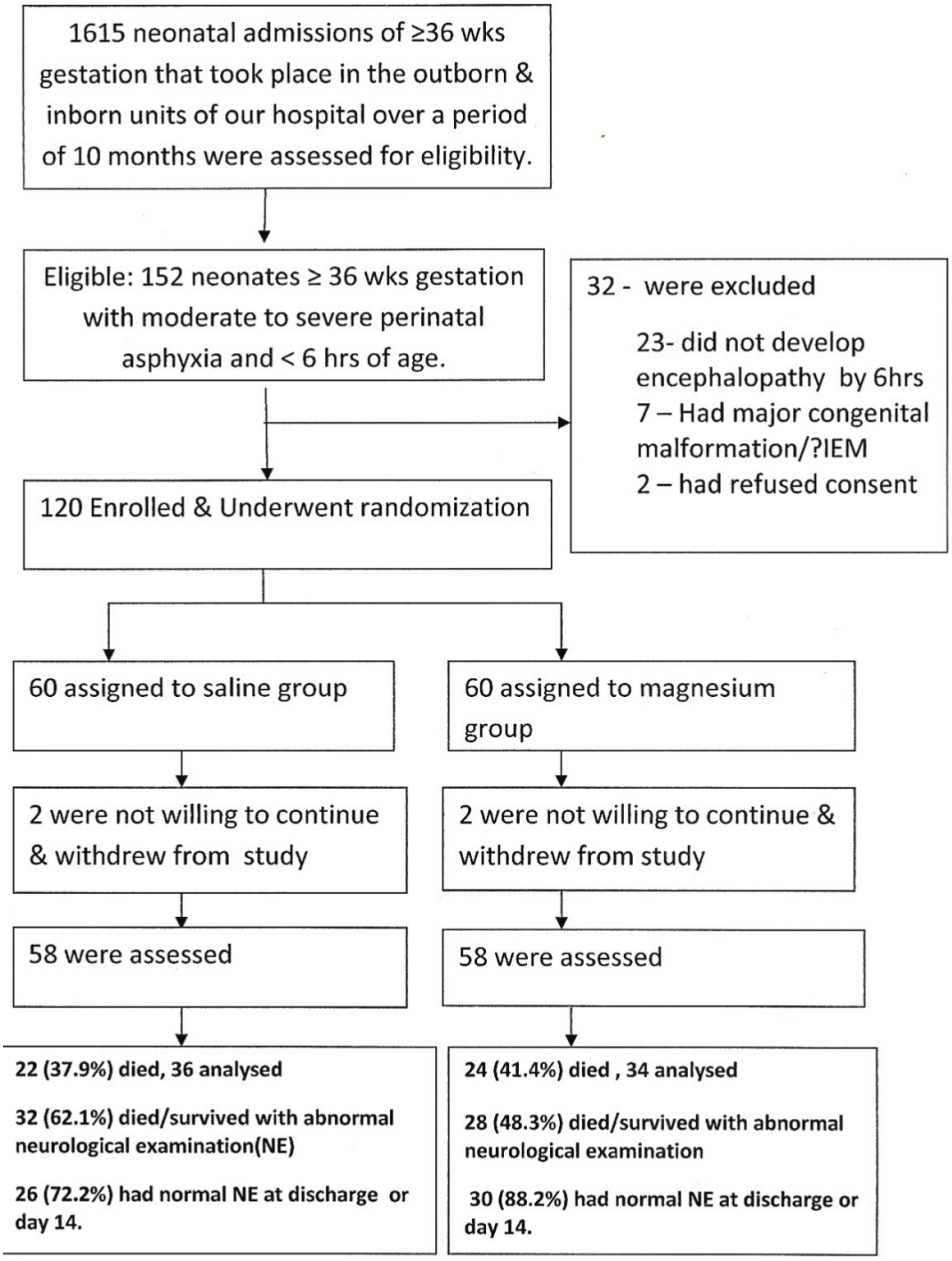


Fig : 1

Table.- 1: Baseline maternal Characteristics

Maternal Characteristics		Group (drug)		Chi square test($\chi 2$)
		Saline, n=58	Magnesium, n=58	
Place of Delivery – no. (%)	Inborn	17 (29.3)	18 (31)	$\chi 2$=0 .04 P =0.84
	Out born	41 (70.7)	40 (69)	
Age of mother in years – no. (%)	< 19	3 (5.2)	1 (1.7)	$\chi 2$=4.88 P =0.18
	20-24	33 (56.9)	44 (75.9)	
	25-29	17 (29.3)	10 (17.2)	
	30-34	5 (8.6)	3 (5.1)	
Parity – no. (%)	One	39 (67.2)	42 (72.4)	$\chi 2$=0.36 P = 0.56
	Two	19 (32.8	16 (27.6)	
Mode of Delivery – no. (%)	Labour natural	40 (69)	40 (69.0)	$\chi 2$=4.06 P = 0.39
	LSCS (emerg.)	10 (17.2)	7 (12.0)	
	Assist. Breech		2 (10.3)	
	Instrumental delivery	8 (13.8)	9 (15.5)	
Meconium Stained Liquor- no. (%)		18 (31)	28(48.3)	$\chi 2$=3.6 P = 0.06
Complications of pregnancy- no.(%) (PIH, GDM)		7 (8.6)	5 (6.9)	$\chi 2$=1.53 P = 0.67

Table -2 : Baseline Neonatal Characteristics

Characteristics		Groups (Drug)		Chi square test($\chi 2$)
		Saline n=58	Magnesium n=58	
Sex – no. (%)	Male	34 (58.6)	37 (63.8)	$\chi 2$=o,32 P = 0.56
	Female	24 (41.4)	21 (36.2	
Gestational age in weeks – no. (%)	36-36 6/7	6 (10.3)	3 (5.2)	$\chi 2$=5.3 P = 0.25
	37- 39 6/7	38 (65.6)	32 (55.2)	
	≥40	14 (24.1)	23 (39.7)	
Age at 1st Inject. – no. (%)	< 3hours	22 (45.1)	15 (25.9)	$\chi 2$=7.1 P = 0.21
	3- 6hhours	33 (56.9)	43 (74.1)	
Mean birth weight in Gms (SD)*		2797.3(445.9)	2878 (386.49)	t=1.04 P=0.29
Resuscitation – no. (%)	BMV only	39 (67.2)	40 (69)	$\chi 2$=1.83 P = 0.4
	BMV & BTV	17 (29.3)	13 (22.4)	
	± chest comp	2 (3.4)	5 (8.6)	
Duration of resuscitation (min)	2 - 5	39 (67.2)	38 (65.5)	$\chi 2$=1.83 P = 0.4
	6 - 10	17 (29.3)	17 (29.3)	
	>10	2 (3.4)	3 (5.2)	
Apgar score – no. (%)	1minute < 3	53 (91.3)	51(87.9)	$\chi 2$=0.21 P = 0.89
	5minute <6	50 (86.2)	48(82.7)	
Onset of seizures within 24 hrs – no. (%)		43 (74.1)	41 (70.7)	P=0.67
HIE stage – no. (%)	Stage 2	47 (81)	46 (79.3)	$\chi 2$=0.05 P = 0.81
	Stage 3	11 (19)	12 (20.7)	
Shock at admission– no. (%)		31(53.4)	37 (63.7)	$\chi 2$=0.05 P = 0.81
Mean arterial pressure (SD)*	before Inject.	41.8 (6.16)	41.3(7.2)	t=0.14 p=0.88
Resp. support at admission – no. (%)	Nil	10 (17.2)	8 (13.8)	$\chi 2$=026 P = 0.87
	O2 by CPAP/hood	26 (44.8)	27 (46.7)	
	Mech. ventilation	22 (37.9)	23 (39.7)	

*SD- Standard deviation, t- student t test

Baseline maternal features like place of delivery, maternal age, parity, mode of delivery and complications during delivery were comparable between the two groups (Table-1).

Baseline neonatal characteristics like sex , gestational age, age at the time of first injection, mean birth weight, need for resuscitation and the methods used, duration of resuscitation, one and five minute Apgar score, onset of seizures, severity of HIE, Mean arterial blood pressure, presence of shock and need for respiratory support were comparable between the two groups (Table – 2).

Baseline maternal characteristics:

Table-3: Place of delivery of neonates in saline and magnesium group

Place of Delivery	Group		Chi square test($\chi 2$)
	Saline, n=58	Magnesium, n=58	
Out born – no. (%)	41 (70.7%)	40 (69%)	$\chi 2$=0 .04 P =0.84
Inborn – no. (%)	17 (29.3%)	18 (31%)	

There were 17(29.3%) and 41 (70.7%) inborn and out born neonates respectively in the saline group. There were 18(31%) inborn and 40 (69%) out born neonates in the magnesium group. There was no significant difference in the number of babies included from inborn and out born deliveries between the saline and magnesium group (Table- 3 , Fig. – 2).

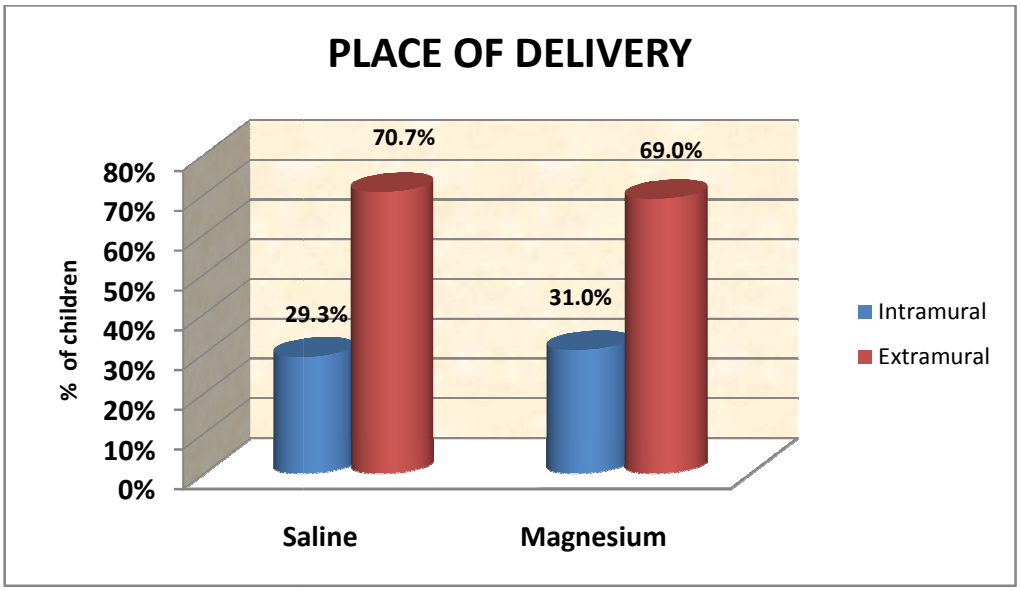


Fig. 2 : Place of delivery of neonates in saline and magnesium group

Table- 4: Age of mothers of neonates included in the study

Age of mothers – no. (%)	Group		Chi square test($\chi 2$)
	Saline, n=58	Magnesium, n= 58	
< 19yrs	3 (5.2%)	1 (1.7%)	$\chi 2$=0 .04 P =0.84
20 - 29 yrs	50 (86%))	54 (93%)	
30 – 34 yrs	5(8.6%)	3 (5.2%)	

There were totally four mothers who were less than 19 years of age. Three in saline and one in magnesium group. Eight mothers were in the age group 30 to 34 years, five in saline and three in magnesium group respectively. Majority of the mothers were in the age group 20 to 29 years in both the groups (Table-4, Fig- 3).

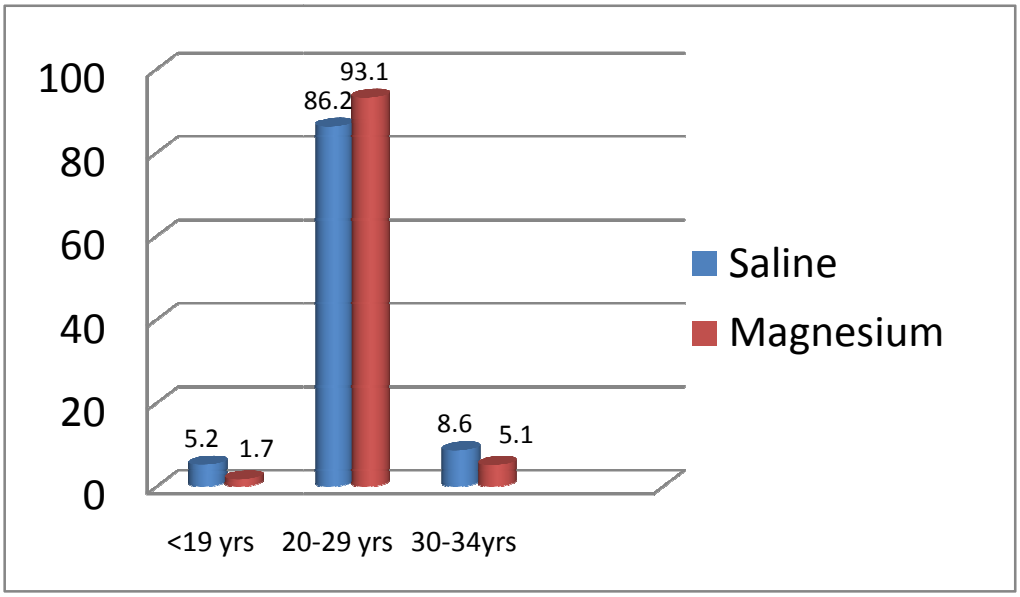


Fig .- 3. Age of mothers of neonates included in the study

Table-5: Mode of delivery in both the groups

Mode of delivery	Group		Chi square test($\chi 2$)
	Saline, n=58	Magnesium, n= 58	
Labour natural	40 (69%)	40 (69%)	$\chi 2$= 4.06 P =0.39
LSCS	10 (17.2%))	7 (12%)	
Breech	0	2(10.3%)	
Instrumental Delivery	8 (13.8%)	9 (3.4%)	

– no. (%)

Most of the neonates included in the study were born normally (40 in both the groups). Ten neonates in saline and six neonates in magnesium group were delivered by emergency LSCS. Instrumental delivery accounted for eight and nine cases in saline and magnesium groups respectively.There was nos ignificant difference regarding mode of delivery between the two groups (Table- 5, Fig 4).

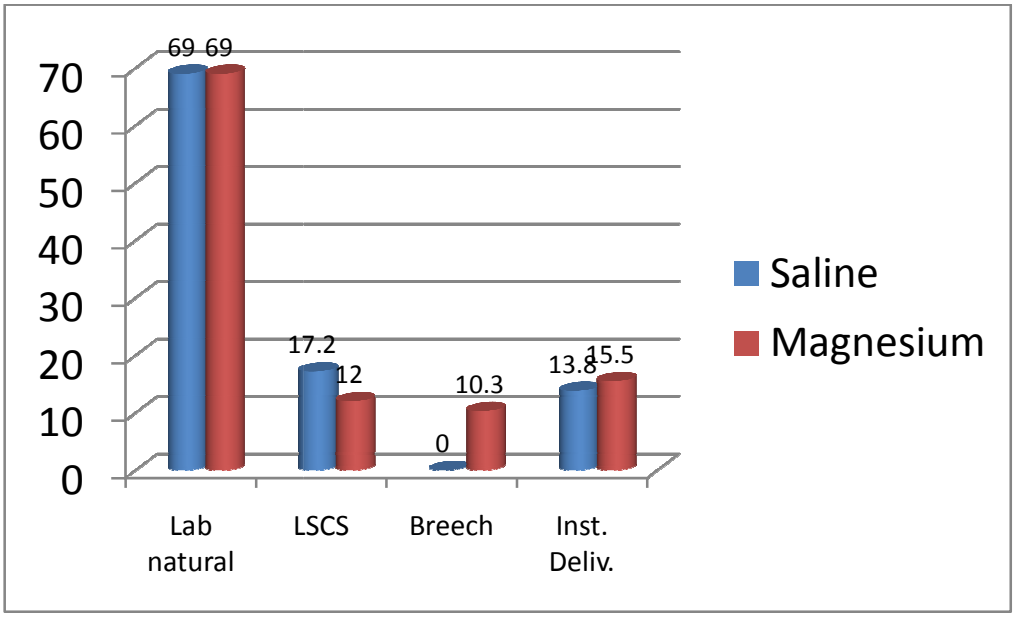


Fig. -4. Mode of delivery in both the groups

Table – 6: Parity of Mothers in both the groups

Parity of mothers	Group		Chi square test($\chi 2$)
	Saline, n=58	Magnesium, n= 58	
Para-1	3 9(67.2%)	42 (72.4%)	$\chi 2$=0.36 P = 0.56
Para-2	19 (32.8%))	16 (27.6%)	

– no. (%)

Most of the mothers were primiparus , 39 (67.2%) and 42 (72.4%) respectively in saline and magnesium group (Table-6, Fig.-5).

History of meconium stained liquor was present in 18 (31%) of neonates in saline group and in 28 (48.3%) in magnesium group. This difference was statistically not significant.

There was no difference in the presence of complications of pregnancy like pregnancy induced hypertension and diabetes mellitus complicating pregnancy (7 in saline and 5 in magnesium group).

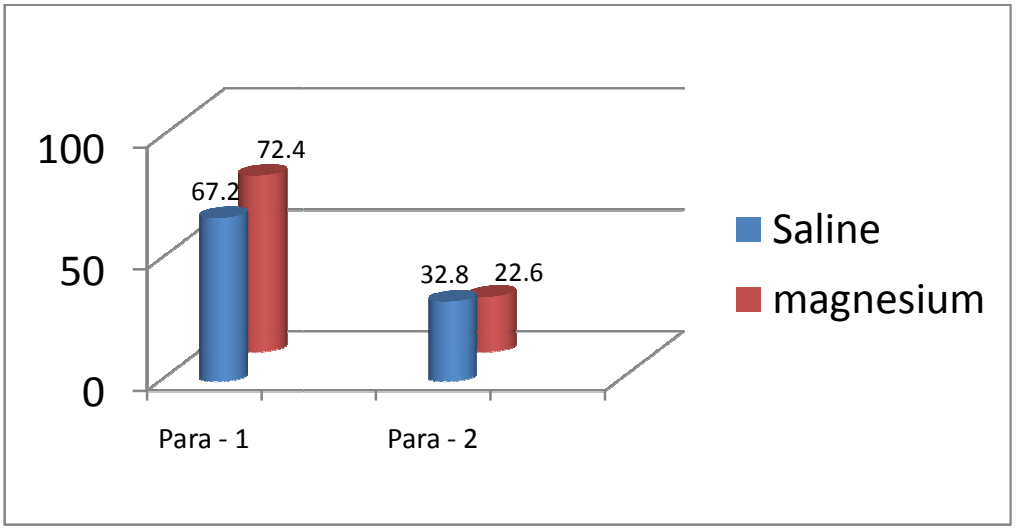
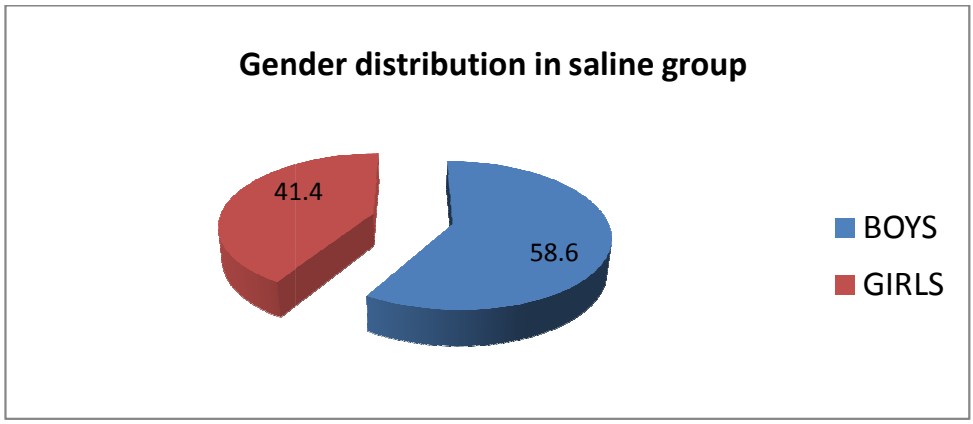


Fig-5: Parity of Mothers in both the groups

Baseline Neonatal Characteristics:

There were totally 71 male and 45 female neonates enroled in the study. Thirty four male and 24 female neonates were included in the saline group. Thirty seven male and 21 female neonates were included in the magnesium group. There was no statistical significance in this regard (Fig.-6) .



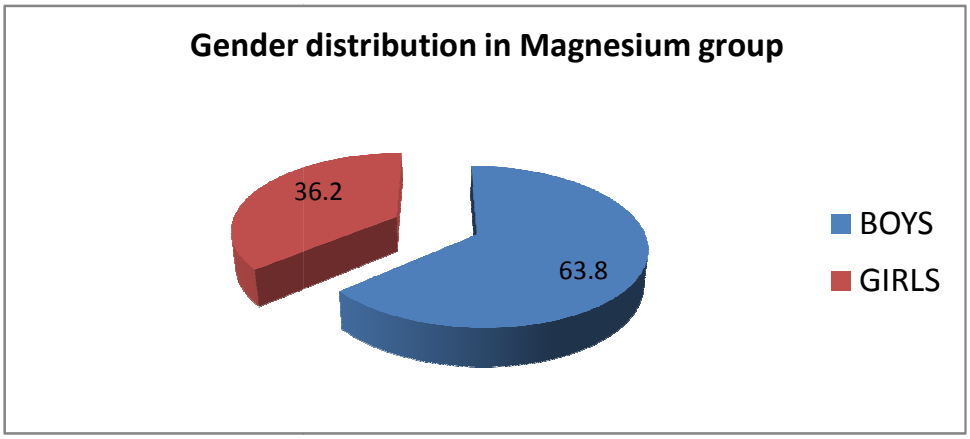


Fig. 6. Distribution of gender in both the groups

Table- 7 : Gestational age of neonates included in the study

Gestational age in weeks	Group		Chi square test($\chi 2$)
	Saline, n=58	Magnesium,n=58	
36 - 36 6/7	6 (10.3%)	3 (5.2%)	$\chi 2$=5.3 P = 0.25
37 – 39 6/7	38 (65.6%))	32 (55.2%)	
≥ 40	14(24.1%)	23(39.7%)	

– no. (%)

Thirty eight (65.6%) and 32(55%) neonates were in the 37 – 39 6/7 weeks gestational age group in the saline and magnesium group respectively. Fourteen (24.1%) and 23 (39.7%) neonates were more than 40 weeks of gestation in the saline and magnesium group. There was no statistically significant difference regarding gestational age between the two groups. (Table- 7, Fig -7).

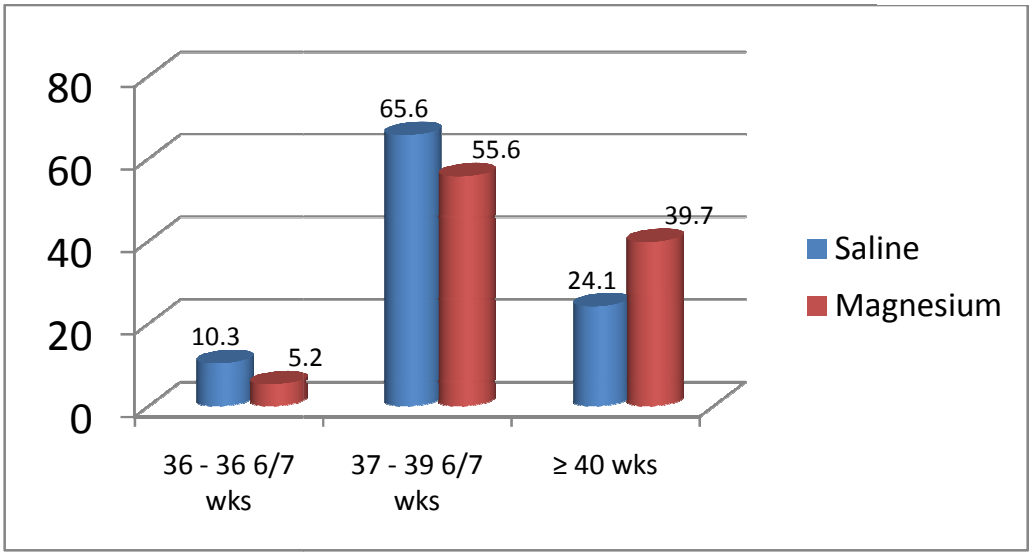


Fig.- 7: Gestational age of neonates included in the study

Table : 8 Age at first injection

Age at 1st injection In hours	Group		Chi square test($\chi 2$)
	Saline, n=58	Magnesium, n=58	
< 3	25(45.1%)	15(25.9%)	$\chi 2=7.1$ P = 0.21
3 -6	33 (56.9%))	43(74.1%)	

– no. (%)

About 60- 70% of neonates in both the groups received their 1st injection between 3 – 6 hours of age . Twenty five (45%) neonates in saline group and 15 (25.9%) in the magnesium group received their 1 st injection at less than 3 hours of age. This difference was not statistically significant. (Table- 8, Fig- 8).

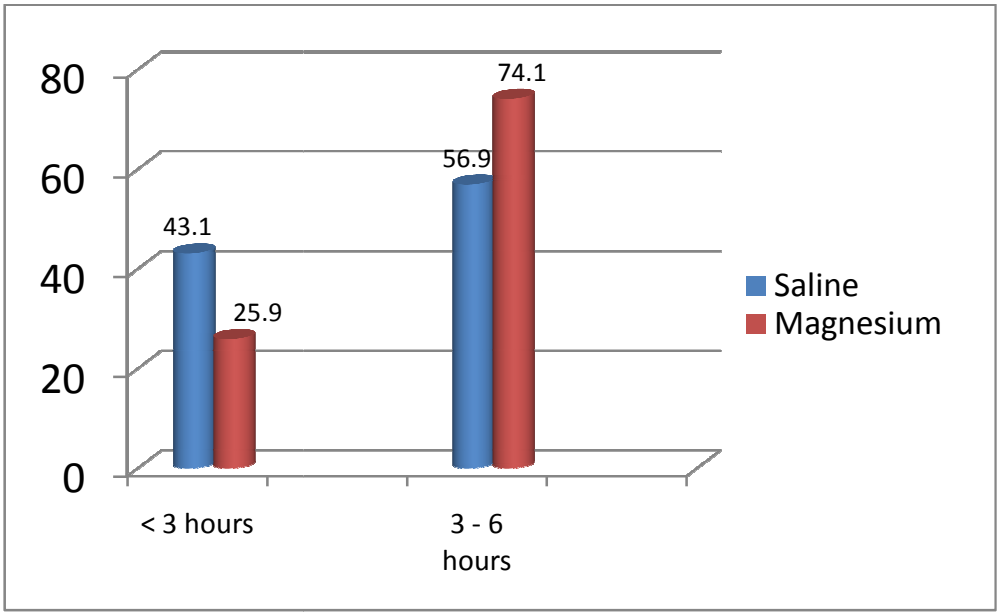


Fig.- 8: Age at first injection

There was no statistically significant difference in the mean birth weight of neonates between the two groups (2797 ±445.9 gms. in saline group and 2878.6 ±386.5gms in magnesium group) Table -2.

All babies had received resuscitation soon after birth. Bag and mask ventilation was the most commonly used method of positive pressure ventilation, 39 (67.2%) in saline and 40 (69%) in magnesium group. Seven babies (2 in saline and 5 in magnesium group) had received ventilation, Chest compression and ± medications.

About 65% of neonates were resuscitated for 2 - 5 minutes. Seventeen (29%) neonates in both the groups were resuscitated for 6 - 10 minutes. Only five neonates had required resuscitation for more than 10 minutes (2 in saline and 3 in magnesium group). The need for resuscitation and the method used and the duration of resuscitation were comparable in both the groups (Table – 2).

Table.- 9 : HIE stage at the time of admission

HIE Stage	Group		Chi square test($\chi 2$)
	Saline, n=58	Magnesium, n=58	
Stage -2	47(81.0%)	46(79.3%)	$\chi 2$=0.05 P = 0.81
Stage -3	11 (19%))	12(20.7%)	

– no. (%)

Regarding Hypoxic ischemic encephalopathy in the two groups recruited, there was no significant difference in the severity of HIE. (47 had HIE stage 2 and 11 had HIE stage 3 in the saline group. Forty six and12 neonates had HIE stage 2 & 3 respectively in the magnesium group. (Table- 9, Fig.- 9).

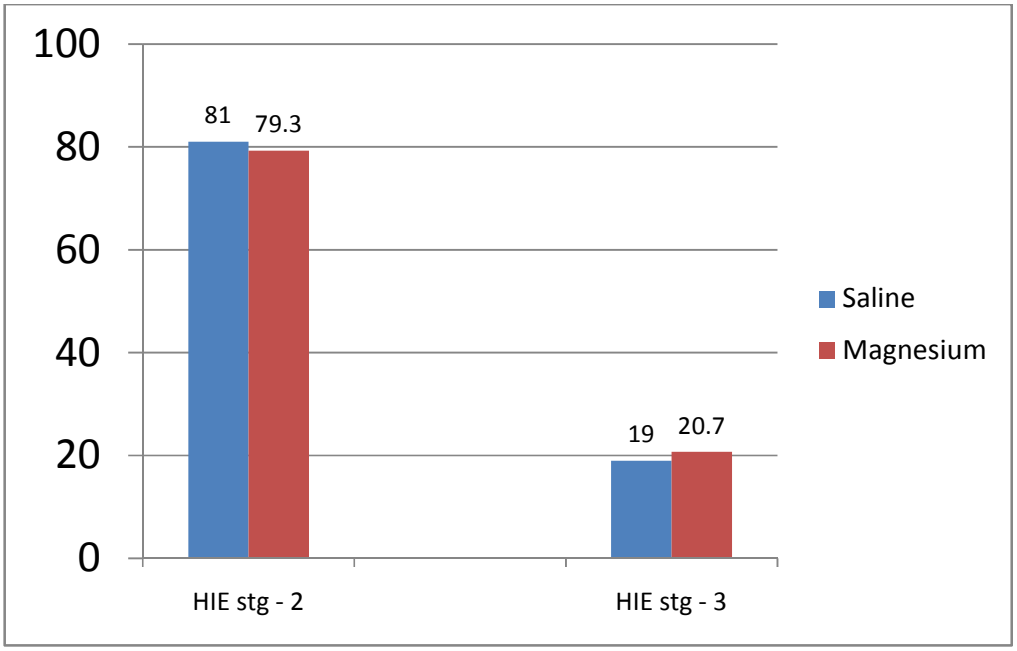


Fig.- 9: HIE stage at the time of admiss

Primary Outcome:

Table – 10 : Primary outcome

Outcome	Groups		Chi square test
	Saline n= 58	magnesium n = 58	
Death – no. (%)	22 (37.9)	24 (41.4)	$\chi 2$=0.14 p=0.70
Death / survival with abnormal neurological examination – no. (%)	32 (62.1)	28 (48.3)	$\chi 2$=0.14 p=0.70
Normal neurological examination@ Discharge/D14* – no. (%)	26 (72.2)	30 (88.2)	$\chi 2$=2.80 p=0.09*

SD- standard deviation, *? Trend towards significance.

1) There were 22 (37.9%) deaths in saline group and 24 (41.4%) deaths in magnesium group. This slight increase in the deaths in magnesium group had no statistical significance.
2) Among the survivors, those with normal neurological examination were more in the magnesium group 30 of 34 (88.2%) than in the saline group 26 of 36 (72.2%). This difference showed a trend towards significance ($\chi 2$=2.80, p=0.09).
3) Combined outcome of death or survival with neurological impairment was more in the saline group, 32 of 58 (62.1%) vs 28 of 58 (48.3%). This difference was statistically not significant (Table – 10, Fig- 10).

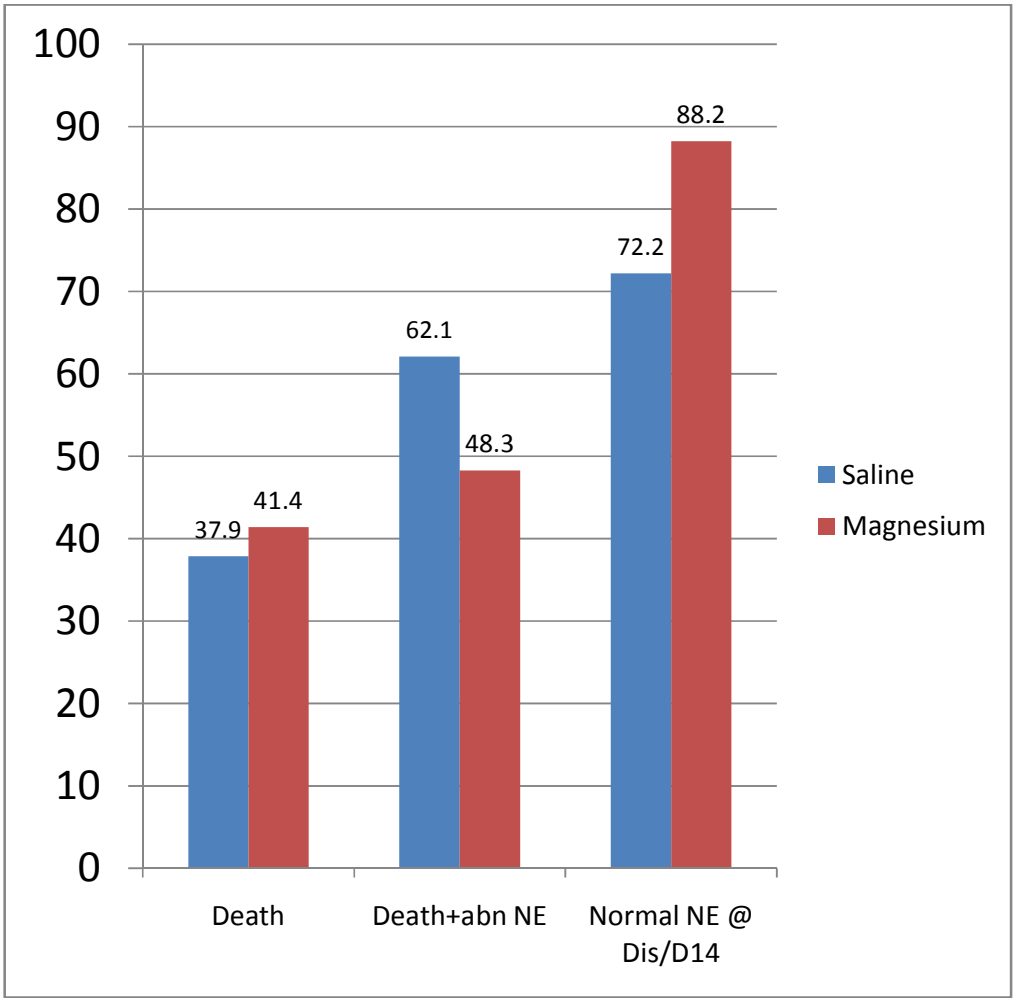


Fig 10. primary outcome

Secondary outcomes:

Table – 11 : Mean age when oral feeding by direct breast feeds (DBF) was initiated and mean age at discharge.

Seconary Outcomes	Groups		Student independent T-test
	Saline n =58	magnesium n = 58	
Mean age of initiation of DBF (SD)	8.24 (6.20)	6.28 (4.42)	t=1.97 p=0.05*
Mean age at discharge (SD)	10.59 (6.28)	8.61 (5.29)	t=1.48 p=0.14
Normal Cranial Ultrasound examination in survivors-no,(%). saline, n=36. Magnesium,n=34.	16 (44.4)	24(70.5)	$\chi 2$=4.01 p=0.05*

SD- standard deviation, *trend towards significance

1) The mean age at which oral feeding by direct breast feeds, were initiated was 8.4 days in saline group and 6.2 days in the magnesium group (t=1.97, p=.05). Similarly the mean age at discharge was less in the magnesium group 8.61 vs 10.59 days (p=0.14). This early initiation of feeding and earlier discharge of neonates in the magnesium group showed a trend towards statistical significance when compared to saline group (Table 11 , Fig.- 15).
2) Ultrasound examination of the cranium among the survivors before discharge, was normal in 16 out of 36 neonates in the saline group and 24 out of 34 in the magnesium group. This difference showed a trend towards statistical significance ($\chi 2$=4.01, p=0.05).

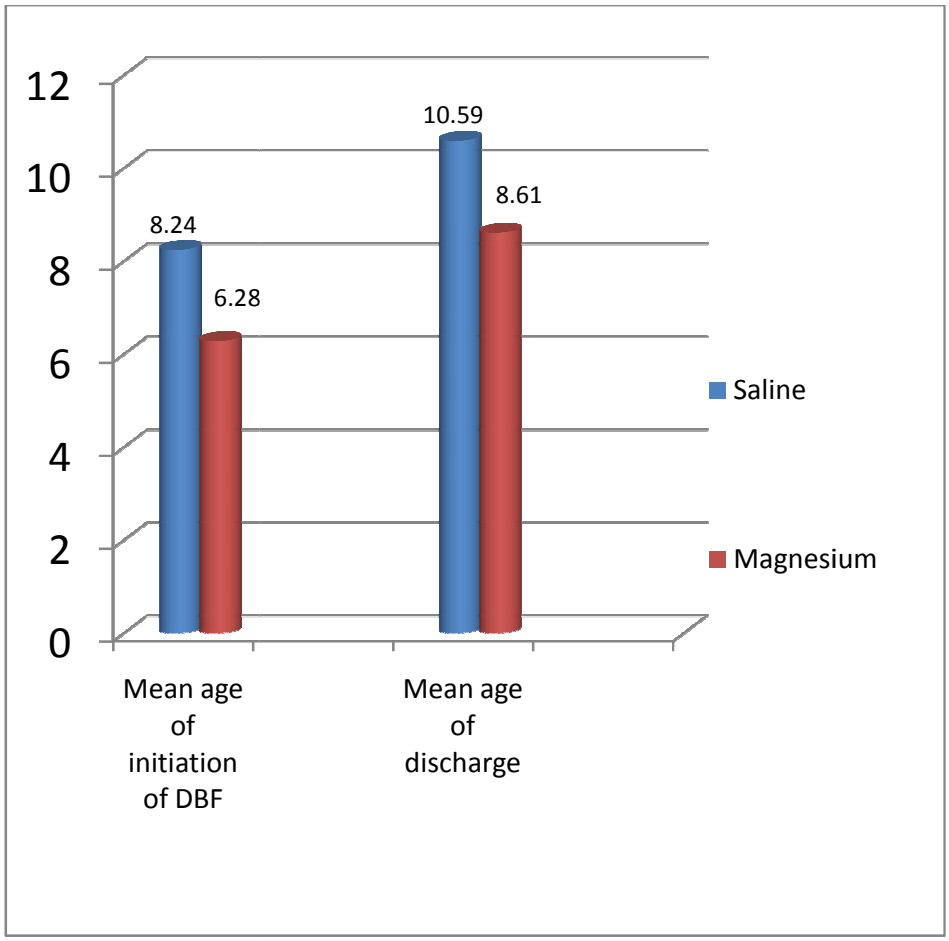


Fig. 11 : Mean age of initiation of DBF & age at discharge

3) An other important secondary outcome in this study was to confirm whether neuroprotective levels of serum magnesium were achieved following IM magnesium sulphate. The results of the analysis clearly showed that the serum magnesium levels were comparable before the 1st injection between the two groups. The levels in the magnesium group were significantly higher (P = 0.001) at 2 , 23 , 26, 47, 50 and at 71 hours after the first injection. The serum magnesium level increased from a mean level of 0.98 to 2.35 mmol/L two hours after the first injection, 1.78 to 2.62mmol/L two hours after the second injection , 1.98 to 2.61mmol/L two hours after the 3rd injection. At 71 hours the level was 2.11 mmol/L. Therefore the mean serum magnesium levels remained more than 1.2 mmol/L throughout the 72 hours after the 1st injection of magnesium. The maximum serum levels were achieved two hours after the 2nd injection (2.62 ±0.59). (Table. 12 , Fig. 12).

Table 12 : Mean serum magnesium levels before and after injection(mmol/L)

Time of measurement of serum magnesium levels		Group		Student independent T-test
		saline	magnesium	
Day 1 n=mean (SD)	Before Inj.	.94 (.21)	.98 (.22)	t=1.03 p=0.30
	2hrs after Inj.	.97 (.20)	2.35 (.55)	t=16.58 p=0.001
Day 2 n= mean (SD)	Before Inj. (23 hrs)	.94 (.19)	1.78 (.50)	t=11.58 p=0.001
	After Inj. (26hrs)	.88 (.20)	2.62 (.59)	t=17.82 p=0.001
Day 3 n= mean (SD)	Before Inj. (47hrs)	.97 (.21)	1.98 (.53)	t=12.50 p=0.001
	After Inj. (50hrs)	.95 (.20)	2.61 (.57)	t=16.79 p=0.001
	71 hrs	.95 (.20)	2.11 (.52)	t=13.68 p=0.001

Fig. 12 : Mean serum magnesium levels before and after injection(mmol/L)

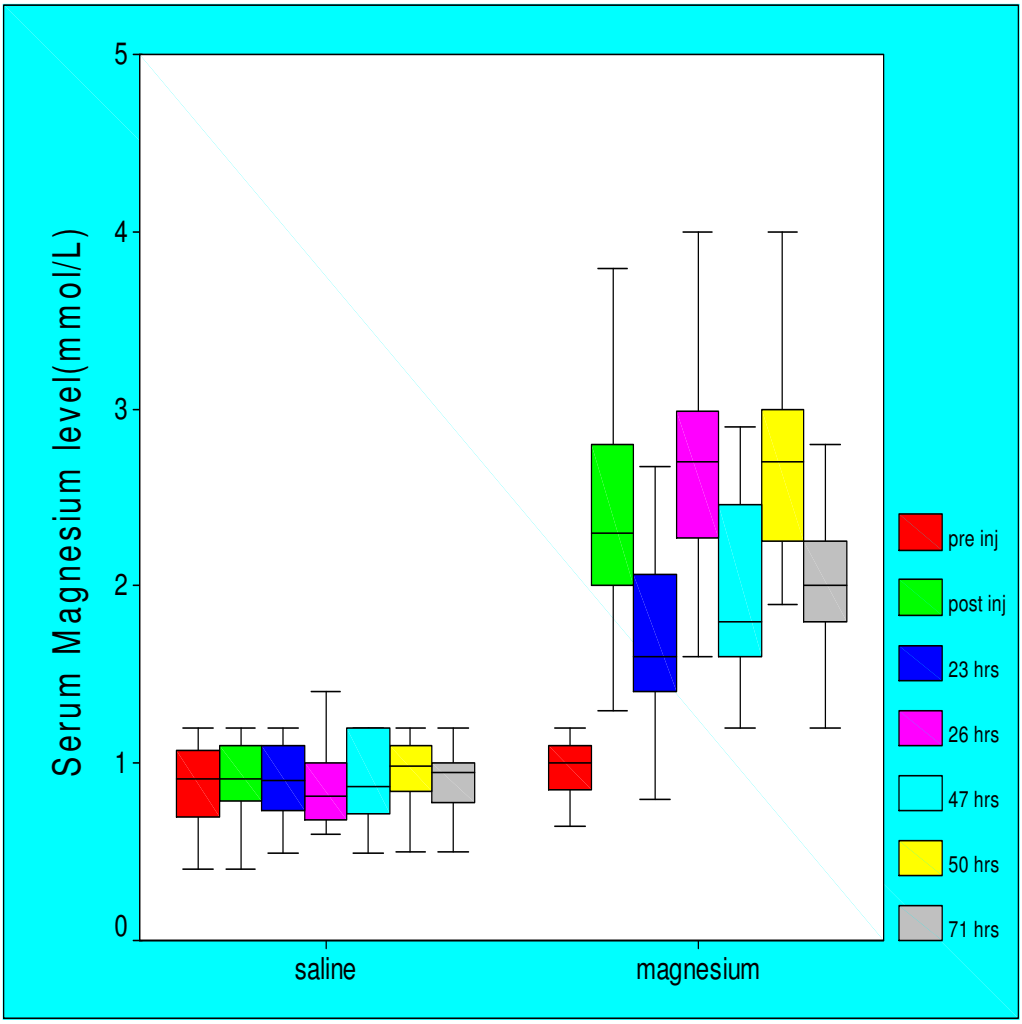


Table -13 : Hospital course

Progress of symptoms		Groups		Chi square test
		Saline n= 58	Magnesium n= 58	
Response of seizures to AED. - no. (%)	Nil	13 (22.4)	19 (32.8)	$\chi 2$=1.58 P = 0.45
	Controlled	32 (55.2)	27 (46.6)	
	refractory	13 (22.4)	12 (20.7)	
Need for mechanical ventilation Day 1 – 4. – no. (%)	Yes	12 (33.3)	9 (25.7)	$\chi 2$=0.49 P = 0.48
	No	24 (66.7)	26 (75.3)	
Mech. Ventilation > 4 days – no. (%)		11 (30.3)	12 (21.9)	$\chi 2$=0.11 P = 0.73
Shock – no. (%)~	Inotrope responsive	25 (44.8)	34 (58.6)	$\chi 2$=4.98 P = 0.08
	Refractory shock	5 (8.6)	3 (5.1)	
CCF/PPHN – no. (%)		4 (6.8)	7(12)	$\chi 2$=0.04 p=0.82
Complication of DIVC – no. (%)		3 (5.1)	4 (6.8)	2=1.93 p=0.37
Gastro Intestinal bleed – no. (%)		15 (25)	13 (22)	$\chi 2$=3.63 p=0.30
Acute kidney injury – no. (%)		9 (15)	13 (22)	$\chi 2$=4.00 p=0.13

*SD- Standard deviation, t- student t test

~ Tachycardia, prolonged CRT, poor peripheral pulses ± hypotension
AED- anti epileptic drugs.

Hospital course of neonates enrolled:

Seizure was a predominant symptom among neonates with moderate to severe HIE. Forty three (74%) neonates in the saline group and 41(70.7%) in magnesium group had seizures within 24 hours. Thirteen (22.4%) and 19(32.8%) in saline and magnesium group respectively did not have seizures after admission. In 32 (56%) neonates in saline group and 27 (46.6%) in magnesium group seizures were controlled with a maximum of two anticonvulsants. Thirteen (22.4%) neonates in saline and 12(20.7%) in magnesium group had refractory seizures (required more than two anticonvulsants for control). There was no statistically significant difference between the two groups regarding presence of seizures, severity and ease of control (Table-13).

Respiratory support at admission in the form of mechanical ventilation (MV) was required for 22(37.9%) in saline group and 23(39.7%) in magnesium group. Twelve (20.6%) in saline and 9 (15.5%) in magnesium group required ventilation from day 2 to day 4. Mechanical ventilation for more than four days was required for 24 (41.3%) neonates in saline and for 26 (44.8%) in magnesium group. The need for mechanical ventilation was not significantly different between the two groups (Table – 13).

Shock as indicated by tachycardia, prolonged CRT, weak peripheral pulses, with or without hypotension was present in 31(53.4%) of neonates in saline group and in 37(63.7%) in magnesium group. In 25(44.8%) of neonates shock was responsive to fluids and/or inotropes in the saline group .Thirty four (58.6%)

neonates responded to inotropes in the magnesium group. Inotrope resistant shock was present in five (8.6%) neonates in saline group and three (5.1%) in magnesium group (Table- 13). There was no statistically significant difference in the course of shock in the two groups

Other complications that were encountered were PPHN, congestive cardiac failure, disseminated intravascular coagulation, gastrointestinal bleed, feed intolerance, and acute kidney injury. These were similar in both the groups (Table- 13).

DISCUSSION

DISCUSSION

Our study showed that the combined outcome of death and survival with abnormal neurological examination was less in neonates treated with IM magnesium sulphate, though this was statistically not significant. Neonates with normal neurological examination at discharge were more in those treated with IM magnesium. This showed a trend towards statistical significance. Similarly the age at initiation of direct breast feeds and age at discharge was less in the magnesium treated group when compared to placebo and this finding too showed a trend towards significance.

The improvement does not seem to be very obvious, as probably magnesium predominantly acts through its NMDA receptor antagonistic property only, and reducing calcium influx by inhibiting glutamate mediated excitotoxicity. There are several other mechanisms of neuronal injury during reperfusion after the asphyxial insult like inflammatory injury due to inflammatory cells (monocytes) attracted to the site of injury, decrease in phosphocreatine /inorganic phosphate ratios leading to secondary energy failure, accumulation of excitotoxic aminoacids, generation of free radicals and activation of proteolytic enzymes like caspases and cystein proteases leading to neuronal apoptosis [11]. Thus a therapy that acts at multiple steps of pathogenesis of neuronal injury like "Therapeutic cooling" may show a better outcome.

In our study we did not use objective methods of assessing improvement like changes in MRI images and changes in EEG findings.

Sonographic examination had shown higher number of normal results in the magnesium treated group (trend towards significance). However sonography though useful as an initial bed side neuroimaging technique, 50% of results in neonates with HIE are normal [60]. Also the results depend on the skill of the personnel performing the sonographic examination. Magnetic resonance imaging and Magnetic resonance spectroscopy are probably the most sensitive imaging technique in the examination of neonates with asphyxial injury [61, 62]. Thus with MRI more neonates with asphyxial brain injury would have been identified and their outcome objectively monitored.

The overall mortality in our study was 40%. This correlates with our unit outcome which was used to plan the sample size. Other authors have reported much lower mortality rates in neonates with asphyxial injury. Bhat MA et al showed an overall mortality of 10% in their study [28]. Shankar S et al had shown 27% mortality in their control group of neonates with asphyxial injury [45]. Thus this high mortality rate could have influenced our study outcome. Basic supportive care which is an important part of management of neonates with asphyxial injury is needed for other therapeutic measures to be effective.

The inclusion criteria in our study had only clinical markers like evidence of fetal distress, Apgar score less than 3 at one minute and need for prolonged duration (more than two minutes) of resuscitation. Neonates who satisfied the above criteria for asphyxia were included in the study only if they developed features of moderate to severe

encephalopathy within six hours of age. This prevented neonates with mild degrees of encephalopathy and those without encephalopathy from being recruited in the study. The higher rate of overall mortality reflects that only those neonates with moderate to severe encephalopathy were included in the study.

Out born neonates were also included in the study as the incidence of asphyxial injury is higher in deliveries that are conducted at level 1 and level 2 settings and this is where our intervention should be implemented.

The neuroprotective role of magnesium has been demonstrated in animal studies by Mayer ML et al, 1984 and by Hoffman DJ, 1994 [15, 16]. Recent studies by. Spandou E et al, 2007 and Cetinkaya M et al, 2011 have shown possible neuroprotective effect in hypoxic rat models [17, 18]. Schendel DE et al and Nelson KB et al had shown decreased incidence of cerebral palsy in preterm neonates whose mothers had received antenatal magnesium sulphate [21, 22]. Rouse DJ et al had shown fetal exposure to magnesium sulphate before anticipated preterm delivery reduced the incidence of cerebral palsy among the survivors [56].

There are only two postnatal human studies that have been carried out to determine the role of intravenous magnesium sulphate in the management of neonates with moderate to severe asphyxial encephalopathy. Ichiba et al had shown that postnatal infusion of Inj. Magnesium sulphate improved the short term outcome namely survival with normal CT scan result of the brain, normal EEG and establishment of oral feeds by 14 days. There was no significant

difference in the duration of clinical seizures, need for assisted ventilation and mortality [26]. However this was not a placebo controlled double blind trial. The same authors in 2006, demonstrated long term benefits of IV magnesium sulphate in neonates with perinatal asphyxia as shown by improved neurodevelopmental outcome at 18 months of age when compared to historical controls [27].

Bhat et al in their randomized placebo controlled trial with postnatal IV magnesium sulphate in neonates with moderate to severe asphyxial injury improved survival with normal neurological examination in the magnesium treated group. They too did not show any difference in the mortality rate between the two groups. A composite measure of normal neurological examination, a normal result in the CT scan of brain, normal EEG pattern and oral feeding through sucking at discharge was significantly better in the magnesium treated group [28].

Ours is the first study of its kind with postnatal IM magnesium sulphate for the treatment of neonates with asphyxial injury. This route of administration of magnesium was considered to enable the intervention to be implemented in the level 2 and level 3 settings where the skill and equipment for IV infusion of magnesium and equipments for adequate monitoring may not be available [36].

A pilot study carried out in our hospital had demonstrated that IM magnesium sulphate given once a day could achieve neuroprotective levels of serum magnesium (as recommended by Levene et al) which can be sustained for 72 hours [unpublished data].

This finding was confirmed in our present study which had shown that mean serum magnesium levels remained above 1.2mmol/L (neuroprotective level) with 3 doses of IM magnesium sulphate 24 hours apart. There were no significant adverse effects like hypotension or respiratory depression when compared to placebo group.

Thus there seems to be a limited but definite role of IM magnesium sulphate in the management of neonates with asphyxial injury. In combination with other accepted neuroprotective modalities of therapy like therapeutic cooling, it may have a synergistic effect.

The strengths of our study were:

1. The robustness of the randomization and blinding of the investigators.
2. Serum magnesium levels were monitored and were found to be within the neuroprotective range
3. A well established Child Developmental Clinic (CDC) performed the neurological examination of the neonates at discharge or on day 14.
4. Those neonates who developed moderate to severe signs of encephalopathy only were included in the study even though clinical markers of asphyxia were used for eligibility criteria.

The limitations of our study were:

1. Inclusion criteria had only clinical markers.
2. Higher overall mortality rates in both the groups could have affected the outcome of the study.
3. Lack of neuroimaging methods like MRI & MRS and EEG monitoring prevented us from identifying many more abnormal neonates and in documenting neurologic improvement or deterioration objectively.

CONCLUSION

CONCLUSION

- Intramuscular magnesium sulphate probably has a neuroprotective role in neonates with asphyxial injury.
- Magnesium does not alter the mortality rate but reduces neurological impairment among survivors.
- Intramuscular magnesium once a day for three days can achieve neuroprotective levels of serum magnesium, which can be maintained for 72 hours.
- Adverse side effects like hypotension or respiratory depression were not a concern with this route and dose.
- Neonates who had normal neurological examination at discharge or on day 14 may need a long-term neurodevelopmental follow up to be definitive about their outcome.
- Though the present study could not convincingly demonstrate the neuroprotective role of magnesium , a larger study with a longer follow up period, with additional support of MRI and EEG technique may give better outcomes.

BIBLIOGRAPHY

BIBLIOGRAPGHY

1) Thornberg E, Thiringer K, Odeback A, Milsom I. Birth asphyxia: incidence, clinical course and outcome in a Swedish population. Acta Paediatr. 1995 Aug; 84 (8) :927-32

2) Hall DR, Smith M, Smith J. Maternal factors contributing to asphyxia neonatorum. J Trop Pediatr 1996;42:192-5.

3) Kinoti SN. Asphyxia of the newborn in east, central and southern Africa. East Afr Med J 1993;70(7):422-33.

4) Bang AT, Bang RA. Diagnosis of causes of childhood deaths in
developing countries by verbal autopsy: suggested criteria. The SEARCHTeam. Bull World Health Organ 1992;70(4):499-507.

5) Report of the National Neonatal Perinatal Database(Nationational Neonatal Forum, India) 2000.

6) Saving Newborn Lives. The state of the world's newborn: a report from saving newborn lives. Washington DC, Save the children: 2001; 1-44.

7) Paneth N. The causes of cerebral palsy Recent evidence. Clin Invest Med. 1993 Apr; 16 (2) :95-102.

8) Robertson CM, Finer NN, Grace MG. School performance of survivors of neonatal encephalopathy associated with birth asphyxia at term. J Pediatr. 1989 May; 114 (5) :753-60.

9) Shankaran S. Shankaran S, Woldt E, Koepke T, Bedard MP, Nandyal R Acute neonatal morbidity and long-term central nervous system sequelae of perinatal asphyxia in term infants. Early Hum Dev. 1991 May ; 25(2):135-48.

10) Dixon G, Badawi N, Kurinczuk JJ, Keogh JM, Silburn SR, Zubrick SR, Stanley FJ. Early developmental outcomes after newborn encephalopathy.Pediatrics. 2002 Jan; 109 (1) :26-33.

11) Volpe JJ. Neurology of the Newborn . Philadelphia, PA: Saunders; 2001. 331- 382p.

12) World Health Organization. The World Health Report 2003. Shaping the Future. Geneva, World Health Organization; 2003.

13) Khashaba MT, Shouman BO. Excitatory amino acids and magnesium sulfate in neonatal asphyxia. H.Brain Dev. 2006 July ; 28(6):375-379.

14) Nowak L, Bregestovski P, Ascher P, Herbet A, Prochiantz A. Magnesium gates glutamate-activated channels in mouse central neurones. Nature. 1984 Feb 2-8; 307 (5950) :462-5.
15) Mayer ML, Westbrook GL, Guthrie PB. Voltage-dependent block by Mg2+ of NMDA responses in spinal cord neurones. Nature. 1984 May 17-23; 309 (5965) :261-3.
16) Hoffman DJ, Marro PJ, McGowan JE, Mishra OP, Delivoria-Papadopoulos M. Protective effect of MgSO4 infusion on NMDA receptor binding characteristics during cerebral cortical hypoxia in the newborn piglet. Brain Res. 1994 Apr 25; 644 (1) :144-9.
17) Spandou E, Soubasi V, Papoutsopoulou S, Augoustides-Savvopoulou P, Loizidis T, Pazaiti A, Karkavelas G, Guiba-Tziampiri O. Neuroprotective effect of long-term MgSO4 administration after cerebral hypoxia-ischemia in newborn rats is related to the severity of brain damage. Reprod Sci. 2007 Oct; 14 (7) :667-77. PubMed PMID:18000228
18) Cetinkaya M, Alkan T, Ozyener F, Kafa IM, Kurt MA, Koksal N. Possible neuroprotective effects of magnesium sulfate and melatonin as both pre- and post-treatment in a neonatal hypoxic-ischemic rat model. Neonatology. 2011; 99 (4) :302-10. PubMed PMID:21135566.
19) Penrice J, Amess PN, PunwaniS, Wylezinska M, Tyszczuk L. Magnesium sulfate after transient hypoxia-ischemia fails to prevent delayed cerebral energy failure in the newborn piglet. Pediatr Res . 1997; 41:443-447.
20) Greenwood K, Cox P. Mehmet H, Penrice J, Amess PN, Cady EB, Wyat JS, Edwards AD. Magnesium sulfate treatment after transient hypoxia-ischemia in the newborn piglet does not protect against cerebral damage. Pediatr Res. 2000; 48::346–350.
21) Schendel DE, Berg CJ, Yeargin-Allsopp M, Boyle CA, Decoufle P. Prenatal magnesium sulfate exposure and the risk for cerebral palsy or mental retardation among very low-birth-weight children aged 3 to 5 years. JAMA. 1996 Dec 11; 276 (22) :1805-10. PubMed PMID:8946900
22) Nelson KB, Grether JK. Can magnesium sulfate reduce the risk of cerebral palsy in very low birthweight infants?. Pediatrics. 1995 Feb; 95 (2) :263-9. PubMed PMID:7838646
23) Penrice J, Amess PN, PunwaniS, Wylezinska M, Tyszczuk L. Magnesium sulfate after transient hypoxia-ischemia fails to

prevent delayed cerebral energy failure in the newborn piglet. Pediatr Res . 1997; 41:443-447.

24) Grether JK, Hoogstrate J. Walsh-Greene E, Nelson KB. Magnesium sulfate for tocolysis and risk of spastic cerebral palsy in premature children born to women without preeclampsia. 2000;183:717–725. American journal of obstetrics and gynecology. 2000; 183:717-725

25) Boyle CA, Yeargin-Allsopp M, Schendel DE, Holmgreen P, Oakley GP. Tocolytic magnesium sulfate exposure and risk of cerebral palsy among children with birth weights less than 1,750 grams. Am J Epidemiol. 2000 Jul 15; 152 (2) :120-4. PubMed PMID:10909948

26) Paneth N, Pinot-Martin J. Neonatal Brain Hemorrhage Study. Magnesium sulfate in labor and risk of neonatal brain lesions and cerebral palsy in low birth weight infants. Pediatrics. 1997; 99(E1).

27) Ichiba H, Tamai H, Negishi H, Ueda T, Kim TJ, Sumida Y, Takahashi Y, Fujinaga H, Minami H, Kansai Magnesium Study Group. Randomized controlled trial of magnesium sulfate infusion for severe birth asphyxia. Pediatr Int. 2002 Oct; 44 (5) :505-9. PubMed PMID:12225549

28) Ichiba H, Yokoi T, Tamai H, Ueda T, Kim TJ, Yamano T. Neurodevelopmental outcome of infants with birth asphyxia treated with magnesium sulfate. Pediatr Int. 2006 Feb; 48 (1) :70-5. PubMed PMID:16490075

29) Bhat MA, Charoo BA, Bhat JI, *et al*. Magnesium sulfate in severe perinatal asphyxia: a randomized, placebo-controlled trial. *Pediatrics* 2009;e764-769**.**

30) Levene M, Blennow M, Whitelaw A, Hankø E, Fellman V, Hartley R. Acute effects of two different doses of magnesium sulphate in infants with birth asphyxia. Arch Dis Child Fetal Neonatal Ed. 1995 Nov; 73 (3) :F174-7.

31) Duley L. , Gülmezoglu AM, Henderson-Smart DJ. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. Cochrane Database of Systematic Reviews. 2003; (2)

32) Caddell JL. Magnesium therapy in premature neonates with apnea neonatorum. J Am Coll Nutr. 1988 Feb; 7 (1) :5-16. PubMed PMID:3343475.

33) Gupta M. Role of Intra-muscular Magnesium Therapy in Mangement of Persistent Apnea and Prevention of Adverse Life Threatening Events. .Indian Pediatrics. 2001; 38:646-649.
34) Pharmacokinetics of injection magnesium sulphate. Available from: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm
35) The American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy and Cerebral Palsy, the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics. Neonatal encephalopathy and cerebral palsy: defining the pathogenesis and pathophysiology. Washington, DC: the American College of Obstetricians and Gynecologists, 2003:1-85.
36) Dilenge ME, Majnemer A, Shevell MI. Long-term developmental outcome of asphyxiated term neonates. J Child Neurol 2001;16(11):781-92.
37) Ellis M, Manandhar N, Shrestha PS, Shrestha L, Manandhar DS, Costello AM. Outcome at 1 year of neonatal encephalopathy in Kathmandu, Nepal. Dev Med Child Neurol.1999;41(10):689-95
38) Lorek A, Takei Y, Cady EB, Wyatt JS, Penrice J, Edwards AD, Peebles D, Wylezinska M, Owen-Reece H, Kirkbride V. Delayed ("secondary") cerebral energy failure after acute hypoxia-ischemia in the newborn piglet: continuous 48-hour studies by phosphorus magnetic resonance spectroscopy. Pediatr Res. 1994 Dec; 36 (6) :699-706.
39) Fellman V, Raivio KO. Reperfusion injury as the mechanism of brain damage after perinatal asphyxia. Pediatr Res1997;41:599-606.
40) Roth SC, Baudin J, Pezzani-Goldsmith M, Townsend J,Reynolds EO, Stewart AL. Relation of deranged neonatal cerebral oxidative metabolism with neurodevelopmental out-come and head circumference at 4 years. Dev Med Child Neurol 1997;39:718-25.
41) Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Arch Neurol 1976;33:696-705.
42) Gonzalez FF, Miller SP. Does perinatal asphyxia impair cognitive function without cerebral palsy? Arch Dis Child Fetal Neonat Ed 2006;91:454-9.
43) Kattwinkel J, Perlman JM, Aziz K, Colby C, Fairchild K, Gallagher J, et al. Neonatal Resuscitation: 2010 American

Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Pediatrics 2010;126(5):e1400-13.
44) Eicher DJ, Wagner CL, Katikaneni LP, Hulsey TC, Bass WT, Kaufman DA, et al. Moderate hypothermia in neonatal encephalopathy: efficacy outcomes. Pediatr Neurol 2005;32:11-7.
45) Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. Lancet 2005;365:663-70.
46) Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med 2005;353:1574-84.
47) Azzopardi D, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med 2009;361:1349-58.
48) Yaari Y, Selzer ME, Pincus JH. Phenytoin: mechanisms of its anticonvulsant action. Ann Neurol 1986;20:171-84.
49) Simpson RE, O'Regan MH, Perkins LM, Phillis JW. Excitatory transmitter amino acid release from the ischemic rat cerebral cortex: effects of adenosine receptor agonists and antagonists. J Neurochem 1992;58:1683-90.
50) Hamada Y, Hayakawa T, Hattori H, Mikawa H. Inhibitor of nitric oxide synthesis reduces hypoxic-ischemic brain damagein the neonatal rat. Pediatr Res 1994;35:10-4
51) Gunn AJ, Mydlar T, Bennet L, Faull RL, Gorter S, Cook C, et al. The neuroprotective actions of a calcium channel antagonist, flunarizine, in the infant rat. Pediatr Res 1989;25:573-6
52) Rosenthal RE, Williams R, Bogaert YE, Getson PR, Fiskum Prevention of postischemic canine neurological injury through potentiation of brain energy metabolism by acetylL-carnitine. Stroke 1992;23:1312-7.
53) Spandou E, Papadopoulou Z, Soubasi V, Karkavelas G, Simeonidou C, Pazaiti A, et al. Erythropoietin prevents long-term sensorimotor deficits and brain injury following neonatal hypoxia-ischemia in rats. Brain Res 2005;1045:22-30.
54) Angeles DM, Wycliffe N, Michelson D, Holshouser BA, Deming DD, Pearce WJ, et al. Use of opioids in asphyxiated

term neonates: effects on neuroimaging and clinical outcome.Pediatr Res 2005;57:873-8.

55) Mami AG, Ballesteros J, Mishra OP, Delivoria-Papadopoulos M. Effects of magnesium sulfate administration during hypoxia on Ca(2+) influx and IP(3) receptor modification in cerebral cortical neuronal nuclei of newborn piglets. Neurochem Res. 2006 Jan;31(1):63-70.

56) Kuban KCK, Leviton A, Pugano M et al. Maternal toxemia is associated with reduced incidence of germinal matrix hemorrhage in premature babies. J Child Neural. 1992;7:70-76.

57) Rouse DJ. Magnesium sulfate for the prevention of cerebral palsy. *AJOG* 2009(June);200(6):610.

58) Gurner TL, Cockburn F, Forfar. Magnesium therapy in neonatal tetany. *Lancet* 1977;**i**:283–4. [RCT]

59) Sibai BM, Graham JM, McCubbin JH. A comparison of intravenous and intramuscular magnesium sulfate regimens in preeclampsia. Am J Obstet Gynecol. 1984 Nov 15; 150 (6) :728-33.

60) Gindler E . Calmagite method of serum magnesium estimation. Clin. Chem 1971;17:662.

61) Stark JE, Seibert JJ. Cerebral artery Doppler ultrasonography for prediction of outcome after perinatal asphyxia. J Ultrasound Med 1994;13:595-600.

62) Barkovich AJ. The encephalopathic neonate: choosing the proper imaging technique. AJNR Am J Neuroradiol 1997;18:1816-20.

63) Barkovich AJ, Westmark KD, Bedi HS, Partridge JC, Ferriero DM, Vigneron DB. Proton spectroscopy and diffusion imaging on the first day of life after perinatal asphyxia: preliminary report. AJNR Am J Neuroradiol 2001;2:1786-94.

Estimation of serum magnesium by Calmagite method

Neonatal neurological examination being performed in CDC

ATOZ *PHARMACEUTICALS PVT. LTD.*

12, Balaji Nagar, Ambattur, Chennai - 600 053. Phone : 26582985, 26585855.

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Analytical Services +++

Form : 39

Certificate of Analysis

Approval No. : 34

(As per Drugs & Cosmetics Act. 1940 and the rules made there under)

ATOZ
Analytical Services +++

1. Name of Manufacturer from whom sample received with Mfg. Lic. No.
M/s. D.CN.KAMALARATHNAM

F12/R/28/73 — 16/04/12

Report No. : — Date :

Mfg. Lic. No. :

2. Reference Number and Date of the letter : — 3.Date of Receipt of the Sample : 28/03/12

4. Name of Drug/Cosmetic/Raw Material Purporting to be contained in the sample : DT: 28/03/2012 **MAGNESIUM SULPHATE INJECTION 50% 2ML AMP (GREEN)**

5. Details of Raw Material/Final Product (in bulk) final Product (in finished pack) : –

(a) Original Manufacturer's / Supplier Name (in case of raw Materials and Drugs repacked) : HINDUSTAN PHARMACEUTICALS BARAUNI 851112

(b) Batch No. / Control No.	(c) Total Quantity represented by the sample	(d) Date of Manufacture	(e) Date of Expiry	(f) Quantity of Sample submitted
118		NOV 11	OCT 13	2 ML - 25 NOS

Results of Analysis — SAMPLE NOT DRAWN BY US

DESCRIPTION	: A CLEAR COLOURLESS LIQUID.		
pH	: 5.54		5.5-7.5
IDENTIFICATION	: COMPLIES AS PER USP		
PARTICULATE MATTER	: COMPLIES AS PER USP		
COMPOSITION	: AS PER ANALYSIS	LABEL CLAIM	LIMIT
MAGNESIUM SULPHATE IP	: 52.6857% w/w.(105.371%)	50% w/w	93%-107%
TEST FOR STERILITY	: COMPLIES AS PER USP		

AZF/07

AZF/07

6.In the opinion of the undersigned the sample referred to above is of standard Quality / is not of standard Quality as defined in the Act and the rules made thereunder for the reasons given below. : COMPLIES AS PER USP

7.Observation : WITH RESPECT TO THE ABOVE TESTS CARRIED OUT

(Person - in Charge of Testing)

ATOZ *PHARMACEUTICALS PVT. LTD.*

12, Balaji Nagar, Ambattur, Chennai - 600 053. Phone : 26582985, 26585855.

ATOZ Analytical Services +++

Form : 39

Certificate of Analysis

(As per Drugs & Cosmetics Act. 1940 and the rules made there under)

Approval No. : 34

ATOZ Analytical Services +++

1. Name of Manufacturer from whom sample received with Mfg. Lic. No.
M/s. **D.CN.KAMALARATHNAM**

Report No. : **F12/R/28/74** Date : **16/04/12**

Mfg. Lic. No. :
2. Reference Number and Date of the letter :
3. Date of Receipt of the Sample : 28/03/12
4. Name of Drug/Cosmetic/Raw Material Purporting to be contained in the sample : **SODIUM CHLORIDE INJECTION I.P**
5. Details of Raw Material/Final Product (in bulk) final Product (in finished pack) : **0.9% SALINE INJ 2ML AMP (RED)**
(a) Original Manufacturer's / Supplier Name (in case of raw Materials and Drugs repacked) : -

SELF

(b) Batch No. / Control No.	(c) Total Quantity represented by the sample	(d) Date of Manufacture	(e) Date of Expiry	(f) Quantity of Sample submitted
TRIAL	-	-	-	**2 ML - 25 NOS**

Results of Analysis — SAMPLE NOT DRAWN BY US

DESCRIPTION	: A CLEAR COLOURLESS LIQUID		
PH	: 4.71 (LIMIT 4.5 TO 7)		
IDENTIFICATION	: POSITIVE FOR THE PRESENCE OF SODIUM CHLORIDE		
COMPOSITION	: AS PER ANALYSIS	LABEL CLAIM	LIMIT
SODIUM CHLORIDE IP	: 0.8211% w/v	0.9%w/v	0.85% - 0.95%
TEST FOR STERILITY	: COMPLIES		
	: TRIAL BATCH		

AZF/07

AZF/07

6. In the opinion of the undersigned the sample referred to above is of ~~standard Quality~~ / ~~is not of standard Quality~~ XXXXXXXXXXXXXX as defined in the Act and the rules made thereunder for the reasons given below. :

7. Observation : **Requisition is made for the above tests only.**

WITH RESPECT TO THE ABOVE TESTS CARRIED OUT

(Person - in Charge of Testing)

RESEARCH INFORMATION SHEET

Title: A randomized controlled trial of Intramuscular Magnesium sulfate in neonates infants with severe Perinatal Asphyxia.

Perinatal Asphyxia in the newborn occurs when there is decreased oxygen & increased carbon dioxide concentration in the blood around the time of delivery. These babies fail to breathe spontaneously at birth & require resuscitation. Severe perinatal asphyxia is injurious to the brain and can result in severe neurological impairment and death.

Injection Magnesium sulphate when given soon after birth seems to have a neuroprotective effect in such asphyxiated babies. Animal studies and few studies in neonates have shown beneficial effect following intravenous magnesium sulphate. The adverse effects following IM Magsulf like hypotension, respiratory depression are less likely with the dose used in the study and are manageable in the NICU set up.

A randomized control trial is being conducted in the Dept of Neonatology IOG maternity hospital & Dept. of Neonatology ICH & HC to find out whether IM Magnesium sulphate given within 6 hrs of life to severely asphyxiated term babies with HIE improves the short term neurological outcome. As your baby was severely asphyxiated at birth with HIE we invite you to join in this study. Your baby will receive either 3 doses of Intramuscular Magsulf or Placebo (Normal saline) over three days as per the study protocol.

There is no compulsion. You can withdraw from the trial at anytime during the study. Your baby will continue to receive routine care given to an asphyxiated baby as per the hospital protocol. During the study, during the analysis of the results and during the publication of the study your identity will not be revealed.

The outcome of the study will be revealed to you after the completion of the study if requested for.

Signature of the Investigator Signature of Parent

Contact Address:

Dr.C.N.Kamalarathnam

II yr, D.M. Neonatology post graduate

I.C.H.&H.C, Egmore, Chennai- 8.

Mobile No.: 9841102746.

Date :

Place : Chennai -8.

Title: A randomized controlled trial of Intramuscular Magnesium sulfate in neonates infants with severe Perinatal Asphyxia.

CONSENT FORM

I Ms/Mr._____ M/O//F/O, B/O _____

Sex_____Hosp. No._____ admitted in the Neonatal ICU of IOG/ICH&HC, Egmore on _____ was explained by the doctor that my baby is diagnosed to have "Severe Perinatal Asphyxia ". This condition requires Neonatal ICU care.

I am willing for my child to be enrolled in the Intramuscular Magnesium Sulphate trial. The doctors have explained to me the nature and the purpose of the trial.

I have given my consent only after completely understanding the details that were explained to me.

I am willing for my baby to be enrolled in this study without any ones compulsion.

I am fully aware that I can withdraw from the trial at any time during the study and routine care for the baby as per the hospital protocol for perinatal asphyxia will be continued.

I have given consent for administering intramuscular Injection of either Magnesium sulphate or Saline as per the study protocol.

I have also given my consent for drawing blood sample for biochemical analysis during the study.

The adverse effects of the drugs were explained to me.

I have given this consent to be enrolled in this study with my full consciousness

Signature of the Investigator **Signature of parent**

Date :

Place: Chennai -8.

ஆராய்ச்சி தகவல் தாள்

தலைப்பு : பிறக்கும் தருவாயில் அதிக அளவில் மூச்சுமுட்டல் ஏற்படும் குழந்தைகளுக்கு ஊசி மூலம் மெக்னீசியம் தருவது பற்றிய ஆராய்ச்சி.

பிறக்கும் தருவாயில் பிராணவாயு குறைவும் கரிமலவாயுவு அதிகம் ஏற்படுவதால் முக்கிய உடல் உறுப்புகளுக்கு பாதிப்பு ஏற்படுகிறது. இவ்வாறான குழந்தைகள் பிறந்தவுடன் தானாக மூச்சுவிட சிரமப்படும் மற்றும் மூச்சூட்டுதலின் அவசியம் ஏற்படும்.

மூச்சு திணறல் ஏற்படும் குழந்தைகளுக்கு மூளை பாதிப்பு ஏற்படும் மற்றும் குழந்தை இறக்கும் வாய்ப்பும் உள்ளது.

இவ்வாறான குழந்தைகளுக்கு மெக்னீசியம் மருந்து அளிப்பதால் மூளை பாதிப்பு குறையும் என்று சில ஆராய்ச்சிகள் கூறுகின்றன. மெக்னீசியம் மருந்து அளிப்பதால் இரத்த அழுத்தம் குறைவும் மற்றும் மூச்சு விடுதலில் பாதிப்பும் ஏற்படலாம். ஆனால் அவை நம் ஆராய்ச்சியில் பயன்படுத்தும் குறைந்த அளவு மருந்தினால் ஏற்படும் வாய்ப்பு குறைவு இந்த பக்கவிளைவுகளை சமாளிக்கும் அளவிற்கு தீவர சிகிச்சைப்பிரிவில் ஏற்பாடு செய்யப்படும்.

மூச்சுமுட்டல் ஏற்பட்டு பிறக்கும் குழந்தைகளை , முதல் ஆறு மணி நேரத்திற்குள் , அரசு தாய்சேய் நல மருத்துவமனையின் பச்சிளங் குழந்தையின் தீவிர சிகிச்சைப் பிரிவில் அனுமதிக்கப்பட்டு மெக்னீசியம் மருந்து அல்லது சலைன் அளித்து ஆராய்ச்சி செய்யப்படும் . உங்கள் குழந்தைக்கு மெக்னீசியம் அல்லது சலைன் கிடைப்பதற்கு சமவாய்ப்பு முறை உபயோகப்படுத்துகிறது.

உங்களுடைய குழந்தைக்கு மூச்சுத்திணறல் ஏற்பட்டுள்ளதால் இந்த ஆராய்ச்சியில் கலந்து கொள்ள அழைக்கிறோம். இதில் எங்களுடைய வற்புறுத்தல் எதுவும் இல்லை.

உங்கள் குழந்தையின் சிகிச்சையில் எந்த பாதிப்பும் இருக்காது.

உங்கள் குழந்தையின் தகவல்களோ அல்லது அடையாளமோ ஆராய்ச்சியின் முடிவில் வெளியிடப்படாது.

இந்த ஆராய்ச்சியின் முடிவு நீங்கள் விரும்பினால் தெரிவிக்கப்படும்.

ஆராய்ச்சியாளரின் கையொப்பம் **பெற்றோர் கையொப்பம்**

டாக்டர்.சி.என்.கமலாரத்னம்
பச்சிளங்குழந்தைகள் பிரிவு
அரசு தாய்சேய் மற்றும் குழந்தைகள் நல மருத்துவமனைகள்
செல்: 98411 02746

ஆராய்ச்சி ஒப்புதல் கடிதம்

தலைப்பு: பிறக்கும் தருவாயில் அதிக அளவில் மூச்சுமூட்டல் ஏற்படும் குழந்தைகளுக்கு ஊசி மூலம் மென்னீஷியம் தருவது பற்றிய ஆராய்ச்சி.

நான் திரு./திருமதி.....
த/பெ./தா/பெ.....B/o.....
உள்நோயாளி எண். ..... அரசினர் தாய்சேய் நல மருத்துவமனையின் / குழந்தைகள் நல மருத்துவமனையின் பச்சிளங்குழந்தைகள் தீவிர சிகிச்சைப் பிரிவில் ..... அன்று அனுமதிக்கப்பட்டுள்ளது. என்னுடைய குழந்தைக்கு பிறக்கும் தருவாயில் மிக மோசமான அளவிற்கு மூச்சுமுட்டல் ஏற்பட்டுள்ளது என்பதையும் அதற்கு தீவிர சிகிச்சை அளிக்கப்பட வேண்டும் என்பதையும் மருத்துவரிடம் இருந்து அறிந்துக் கொண்டேன்.

நான் என் குழந்தையை ஊசி மூலம் மெக்னீஷியம் அளிக்கும் ஆராய்ச்சியில் ஈடுபடுத்திக் கொள்ள சம்மதிக்கிறேன்.

ஆராய்ச்சி குறித்த தகவல்தாள் எனக்கு வழங்கப்பட்டது.

இவ்வாராய்ச்சியின் விளக்கங்களைப் பெற்ற பிறகே நான் சம்மதிக்கிறேன்.

நான் இந்த ஆராய்ச்சியில் இருந்து எந்த நேரமும் விளக்கிக் கொள்ளலாம் என்பதையும் மருத்துவரிடம் இருந்து அறிந்து கொண்டேன்.

இந்த ஆராய்ச்சியின் படி என்னுடைய குழந்தைக்கு மெக்னீஷியமோ அல்லது சலைன் (Saline) அளிக்க சம்மதிக்கிறேன்.

என்னுடைய குழந்தையிடமிருந்து ஆராய்ச்சிக்காக இரத்த பரிசோதனை செய்ய சம்மதிக்கிறேன்.

இந்த ஆராய்ச்சியிலும் மருந்தினாலும் ஏற்படும் விளைவுகளும், பக்க விளைவுகளும் பற்றி எனக்கு விளக்கப்பட்டுள்ளது.

என்னுடைய குழந்தையை இந்த ஆராய்ச்சியில் ஈடுபடுத்திக் கொள்ள முழு சம்மதத்தை அளிக்கிறேன்.

ஆராய்ச்சியாளரின் கையொப்பம் **பெற்றோர் கையொப்பம்**

டாக்டர் C.N. கமலரத்னம்
பச்சிளங்குழந்தைகள் பிரிவு
அரசு தாய்சேய் மற்றும் குழந்தைகள் நல மருத்துவமனைகள்.

இடம் :
தேதி :

Intramuscular magnesium sulphate (Inj. Magsulf.) in perinatal asphyxia Study

Proforma IP. No._____

1) Sl. No. ☐☐ **Name:** **Date:**

2) Age in Hrs: ☐☐ Address: S/O, D/O

3) Sex: ☐
1—male, 2—female **Mob. No.:**

4) Place of delivery: ☐ **1- intramural, 2- extramural**

5) Maternal details:

a) age (yrs) ☐☐

b) Para ☐

c) Mode of delivery ☐ **DOD;** ☐☐☐, **Time** ☐☐, **AM/PM**

1—natural, 2—Forceps, 3- Breech, 4—LSCS (emergent), 5- LSCS (Elective)

d) FHR < 100 ☐ **1- yes, 2- no**

e) MSL ☐ **1—yes, 2-- No**

f) Fetal late deceleration ☐ **1—yes, 2—no**

g) Intrapartum complication ☐ 0- Nil,1- cord prolapse,2- utr. rupture,3-others

h) Antenatal magsulf therapy : ☐ **1- yes, 2-No, Dose if yes :**

i) Duration of labour ☐☐ **hrs** (1st & 2nd stage included).

j) H/O DM,PIH , chronic CVS, renal ,GI problems: ☐ **1- yes, 2-no**

5) Baby

a) Gestational age : ☐☐ **Wks.** ☐ **Days**

b) Birth wt : ☐☐☐☐ **gms**

c) Length ☐☐ **cms**

d) OFC ☐☐ **cms**

e) **Apgar: 1min** ☐ , **5min** ☐ ,**10min** ☐

f) **Resuscitaion** ☐ 1-BMV,2- TBV **f) Duration of resuscitation:** ☐☐ **min**

h) Seizures ☐ **1- yes, 2 no. , i) HIE** ☐ **II / III** (refer monitoring sheet)

6) **INJECTION** ☐ 0.5ml / kg div into two equal half, deep IM in both thighs

Dose	**date & time**
0	
24hrs	
48hrs	

Blood sample	**Date & time of sample**	**Sr magnesium levels**
Pre inj Magsulf		
1 hr post Injection		
23hrs		
25 hrs		
47 hrs		
49hrs		
72hrs		

Date										
SGOT										
SGPT										
Na+										
K+										
HCO3										
Ca++										
Urea										
Creat										
U/S cranium										
EEG										
CT/MRI										
CBC-1										
2										

Magsulf Study – VITALS Chart

Sl. NO: **Name:** **Day-1/ Day-2/Day-3**

Day- 1 Date &Time Parameters	Before inj.	15 Min	30 Min	45 min	60 min	4 Hrs	8 hrs	12 Hrs	16 Hrs	20 hrs	24 Hrs
Heart rate/min											
Resp. rate/min											
CRT <3-1, >3-2											
BP: Sys/di MAP											

Day-2 Date & time Parameters	Before inj.	15 Min	30 Min	45 min	60 min	4 Hrs	8 hrs	12 Hrs	16 Hrs	20 hrs	24 Hrs
Heart rate/min											
Resp. rate/min											
CRT <3-1, >3-2											
BP: Sys/di MAP											
Day-3 Date & time Parameters	Before inj.	15 Min	30 Min	45 min	60 min	4 Hrs	8 hrs	12 Hrs	16 Hrs	20 hrs	24 Hrs
Heart rate/min											
Resp. rate/min											
CRT <3-1, >3-2											
BP: Sys/di MAP											

HIE Staging (Modified Sarnat& Sarnat staging)

Category	Hypoxic Ischemic Encephalopathy	
	Moderate	Severe
Level of consciousness	Lethargic	Stupor/ coma
Spontaneous activity	Decreased	No activity
Posture	Distal flexion or complete extension	Decerebrate state
Tone	Hypotonia- focal/general	Flaccid
Primitive reflexes		
Suck	Weak	Absent
Moro	Incomplete	Absent
Autonomic system.		
Pupils	Constricted	Deviated , dilated or nonreactive to light
Heart rate	Bradycardia	Variable
respiration	Periodic breathing	Apnea
Seizures	present	Absent

The number of moderate or severe signs determine the extent of encephalopathy; if signs are equally distributed, the designation is based on the level of consciousness.

Daily monitoring sheet: Name **Hosp No** **Sl. NO**

Examination Days & date	1		2		3		4		5		6		7	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
CNS														
Seizures, 1yes,2-no														
LOC 1-lethargy 2-stupor/coma 3- normal														
Spon. Activity 1-decreased 2- No activity 3-normal/														
Posture 1-dist. Flexion 2-decerebrate														
Tone 1-hypotonia 2-flaccid 3normal/hyper														
Primitive reflexes														
Suck 1-weak, 2-absent														
Moro 1-incomplete 2-absent														
Aut. system														
Pupils 1-constricted 2-dilated/NR														
Heart rate 1-bradicardia 2-variable														
Respiration 1per.breathing 2apnea														
HIE STAGE 1/2/3														
Resp support 1-nil, 2-O2, 3-CPAP, 4- IPPV														

Examination Days & date	1		2		3		4		5		6		7	
CVS	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Shock-1/2 1-yes. 2No														
1- fluid bolus 2- Inotropes- D/DO/AD														
CCF-1/2 1-yes, 2-No														
Arrhythmias 1-yes, 2-No														
Hematology 1-N, 2-↓plat., 3- DIC														
Metabolic 1-↓cal, 2↓Glu, 3- acidosis														
Urine output 1-N,2- oliguri, 3-anuria														
Weight(gms)														
Feeds 1-Tubefeeds 2-Paladay 3-DBF														
Outcome 1-Death 2-Survival with sequale 3- AMA /withdrawal														

Report of Neurological examination at discharge / at 14 days of life:

no	Sl. NO	sex	gest. Age	age in hrs	Pl of Del	age	para	DODel	mod.of del	FHR	MSL	Late decel	Int. part. Compl.
1	A1	2	4	2	2	3	2	4/16/2012	1	4	1	3	1
2	A2	2	4	4	1	2	1	4/18/2012	3	2	1	2	1
3	A3	2	4	4	2	2	1	4/20/2012	1	4	1	3	5
4	A4	2	4	3	1	2	1	4/21/2012	5	2	2	2	1
5	A5	1	4	5	2	3	2	4/25/2012	1	4	2	3	1
6	A6	1	2	5	2	3	2	4/25/2012	3	1	2	2	1
7	A7	2	4	5	2	4	2	4/28/2012	1	4	2	3	1
8	A8	1	4	3	2	2	2	5/2/2012	1	4	2	3	1
9	A9	1	5	3	2	2	1	5/5/2012	5	4	2	3	1
10	A10	2	5	1	1	2	3	5/4/2012	5	2	2	2	1
11	A11	2	5	6	2	2	2	5/9/2012	1	4	1	3	1
12	A12	1	2	2	1	2	2	5/8/2012	5	2	2	2	1
13	A13	1	4	1	1	4	2	5/7/2012	5	4	1	3	1
14	A14	2	3	3	2	2	1	5/27/2012	1	4	2	3	1
15	A15	2	4	1	1	2	1	5/10/2012	1	2	1	2	1
16	A16	1	4	6	1	2	1	5/19/2012	1	2	2	2	1
17	A17	2	4	1	1	3	2	5/25/2012	4	2	2	2	1
18	A18	1	5	1	1	2	1	5/27/2012	1	2	2	2	1
19	A19	2	4	6	2	3	2	5/27/2012	3	3	1	3	1
20	A20	1	1	3	2	2	2	5/29/2012	1	4	2	3	1
21	A21	1	5	4	2	2	1	6/1/2012	1	2	2	2	1
22	A22	1	3	4	1	3	1	6/1/2012	1	2	2	2	1
23	A23	1	4	2	2	2	1	6/8/2012	1	2	1	3	1
24	A24	2	3	3	2	3	1	6/8/2012	1	4	1	3	1
25	A25	2	4	3	2	2	1	6/8/2012	1	4	2	3	1
26	A26	1	4	3	2	2	1	6/14/2012	1	4	2	3	1
27	A27	2	5	3	1	2	1	6/12/2012	1	2	2	2	1
28	A28	1	5	2	1	3	1	6/14/2012	5	2	2	2	1
29	A29	2	4	3	2	1	1	6/15/2012	1	4	2	3	1
30	A30	2	4	3	2	3	1	6/22/2012	1	4	2	3	1
31	A31	1	1	4	2	2	1	6/29/2012	5	4	1	3	1
32	A32	1	5	3	2	2	2	6/26/2012	1	4	2	3	1
33	A33	1	1	5	1	2	1	6/27/2012	1	2	2	2	1
34	A34	1	1	4	2	2	2	6/27/2012	4	4	2	3	1
36	A36	1	5	3	2	3	2	7/5/2012	1	4	2	3	1
37	A37	1	2	4	2	2	1	7/8/2012	1	4	2	3	1
38	A38	1	3	3	1	3	2	7/9/2012	1	2	2	2	1
39	A39	1	4	3	2	3	2	7/10/2012	5	4	2	3	1
40	A40	2	1	1	1	4	2	8/31/2012	1	1	1	1	4

no	AN Magsulf	Dur. LaborO	Obstet. Prob	Med. Prob	B. wt	Length	wt/ lt-PI	OFC-cms	apgar 1	apgar 5	apgar 10	resuscitation	duration(min)
1	0	1	1	2	3100	48	>2.5	34				1	1
2	0	3	1	2	2850	48		32	2	5		2	1
3	0	3	1	2	2960	49		33.5	2	2	2	3	3
4	0	3	1	2	3015	51		35	2	6		1	1
5	0	1	2	2	3000	49		34				1	2
6	0	1	2	2	2390	48		34	2	6		1	2
7	0	1	2	2	3600	52		34	2	5		1	2
8	0	1	1	2	3250	49		33	2	5		1	1
9	0	2	1	2	2645	48		33	2	5		1	1
10	0	3	1	2	3025	51		32.5	2	4	5	3	2
11	0	1	1	2	2500	47		34	2			1	3
12	0	2	1	2	3330	49		34	2	5	5	1	1
13	0	2	1	2	2500	51		34	2	4	4	3	2
14	0	1	1	2	2200	45		32	2	6		1	1
15	0	2	1	2	2250	49		33.5	1	4	5	3	2
16	0	3	1	2	3250	51		34	2	6	7	1	1
17	0	1	1	2	3750	51		34	0	0	4	3	3
18	0	3	1	2	3350	50		33	3	4	7	1	1
19	0	6	3	2	2400	49		32	3	7		1	1
20	0	1	1	2	4025	53		36	2			1	2
21	0	4	1	2	2970	50		33	2	2	7	1	1
22	0	3	1	2	2750	49		33	2	5	7	1	1
23	0	3	2	2	3000	51		34	2	6		1	1
24	0	2	2	2	2900	52		34	2			1	1
25	0	1	1	2	2750	51		34.5	2			1	2
26	0	6	1	2	3170	50		34	2	4		1	1
27	0	1	1	2	2500	46		32	2	3	7	3	1
28	0	3	1	2	3575	52		36	2	6	7	1	1
29	0	3	1	2	2930	54		33.5		5		1	1
30	0	3	1	2	3250	52		34	2			1	1
31	0	3	1	2	2860	50		34	1	4	7	3	1
32	0	2	1	2	3100	52		34	2	5		1	1
33	0	3	1	2	2250	46		32	1	3		3	2
34	0	5	1	2	2660	53		34	1			3	2
36	0	3	1	2	2980	53		35	3			1	1
37	0	2	1	2	2750	50		34.5	2	5		1	2
38	0	3	1	2	3100	51		33.5	3	5	5	3	2
39	0	3	1	2	2900	50		33.5	1	2	3	3	2
40	0	3	2	2	2000	49		32	0	1	2	3	2

no	seizures < 6hrs	HIE	GROUP(drug)	Sr Mg preinj	post inj	23 hrs	26hrs	47hrs	50hrs	71hrs	Onset of seizure within 24 hrs	course of seizures	HIE-D!
1	2	4	0	0.63	1.1	1.2	1.1	1.2	1.08	1	2	1	3
2	2	2	1	1.2	2.25	1.7	3.2	2.5	3	2	1	1	3
3	1	3	0	1.2	1.2						1	3	3
4	1	2	0	1.1	1.2	1		1.2	1.1	1	1	3	2
5	1	3	1	0.9	2.3	2.14	3	1.77	3.5	2.1	2	1	2
6	1	3	1	1.1	3.79	2.67	4	2.47	4	2.59	1	2	3
7	1	2	0	1.2	1.1	1.26	1.3	1.34		1.1	1	3	2
8	1	3	0	1.1	1.2	1.3		1.15		1.2	1	2	3
9	1	2	0	1.1	0.8	0.77	0.73	1.2	0.97	1.2	1	2	2
10	2	3	1	0.77	2.34	2.4	3.25	3.29		2.92	2	1	3
11	1	2	1	0.64	2.5	2.3	2.9	2.45	3	3.2	1	2	2
12	2	2	1	0.78	3.3	2.18	3.6	2.9	3.5	2.8	2	1	2
13	2	2	0	0.73	0.79	1.1	1.2	1.1	1.2	0.98	1	1	2
14	1	2	0	0.9	0.94	0.9	0.8	0.8	0.98	0.9	1	2	2
15	1	2	0	0.77	0.87	0.73	0.64	0.93	0.81	0.94	1	2	2
16	1	2	1	0.68	2.7	2	3.2	2.9	3.9	2.1	1	2	2
17	1	3	1	0.69	2.55						2	1	3
18	1	2	1	0.74	1.97	1.6	2.28	2.1	2.8	1.89	1	2	2
19	1	2	0	0.97	0.88	0.64		0.77			1	2	2
20	1	2	0	0.79	0.89	1.2	1.1	0.81	0.89	0.98	1	3	2
21	1	2	1	0.64	3	1.7		1.8	2	1.8	1	2	2
22	1	2	1	1.1	2.9	2	2.9	1.6	2.7	2.8	1	2	2
23	2	3	0	0.5	0.71	1.1	1				2	1	3
24	2	3	1	0.78	2.2	2.3	2.7	2.6	3	2.7	2	1	3
25	1	2	1	0.75	3.2	3.2	3.7	2.6			1	1	2
26	1	2	0	1.2	1.2	0.9	0.8	1.1	0.9	1.2	2	2	2
27	2	2	1	0.9	2.1	1.5	2.5	1.5	2.5	2	1	1	2
28	1	2	0	0.98	1	0.7	0.7	1.2	1	0.96	1	2	2
29	1	2	0	0.9	0.86	1.2	0.98	1.2		1.1	1	3	2
30	1	2	1	0.98	2.5	2.1		2.6		3.2	1	3	2
31	1	2	0	0.9		1	1	1.2		1.1	2	3	2
32	2	2	1	1.2		3					2	2	2
33	2	3	1	1.2	2.7	2.4	2.9				2	1	3
34	1	2	1	1.2	3.5	2	3.3	2.5		2.1	1	3	3
36	1	2	0	1	0.98	0.74	0.88	1.1			1	2	2
37	1	2	0	1.1	0.98	0.74					1	3	2
38	1	2	0	0.9	1.1	0.9	0.7	0.9		0.8	1	2	2
39	2	3	1	0.74	2.2	2	3.3				2	1	3
40	2	3	0	0.9	1.2						2	1	3

no	HIE D2	HIE-D3	HIE D4 onwards	Resp support @ Adm	MV after 24hrs-day4	days of MV	MAP bef Inj 0hrs	MAP aft Inj	bef inj 24hrs	aft inj 26hrs	bef inj 48hrs	aft inj 50hrs	Shock
1	2	2	3	3		4	44	41	39	40	40	34	1
2	2	2	2	1	2		34	42	38	47	44	45	1
3	3			3		2	30	36	48	42			1
4	2	0	0	1	2		44	48	50	52	48	46	2
5	1	1	0	1	2		43	41	44	41	42	42	2
6	3	1	0	3		2	34	33	44	42	46	44	1
7	3	3	2	2	1	5	54	48	38	54	55	49	2
8	3	3	3	3		4	44	42	38	42	36	34	1
9	2	2	0	2	2		40	42	40	44	44	42	2
10	3	3	2	3		4	44	47	44	46	46	47	1
11	2	3	3	3		5	40	42	47	49	44	53	1
12	2	1	1	2	2		50	48	44	45	46	49	2
13	2	3	3	3		5	36	40	36	34	34	32	1
14	1	1	1	2	2		44	44	42	44	46	44	2
15	2	2	2	3		1	47	46	48	46	46	48	2
16	2	2	0	1	2		42	44	40	42	39	42	2
17				3		1	32	32					1
18	2	2	0	2	2		42	40	48	50	46	44	2
19	1	0	0	1	2		40	45	44	46	42	48	2
20	2	2	2	1	1	2	42	44	42	40	46	48	1
21	2	1	0	2	2		40	44	42	44	46	48	2
22	2	2	0	1	2		48	44	40	44	44	46	2
23	3			3		2	36	38	40				1
24	3	3	3	3		4	30	36	34	35	32	34	1
25	3			2	2		38	40	42	40			2
26	2	3	0	2	1	2	42	44	44	40	40	42	2
27	2	1	0	2	2		46	44	48	46	44	46	2
28	2	1	0	2	2		40	44	42	42	45	42	2
29	2	2	1	2	2		36	42	44	42	44	42	1
30	2	2	2	2	2		32	34	36	38	40	42	1
31	2	2	1	2	2		44	42	40	42	40	42	2
32	2	0	0	1	2		40	44	42	44			2
33	3			3		2	36	40	34	36			1
34	3	3	3	3		8	41	40	43	45	45	44	1
36	2	3	3	2	1	1	44	42	34	32	34	36	1
37	3	3		2	1	1	42	40	40	42			1
38	2	0	0	3		1	41	44	42	44	40	44	2
39	3	3		3		3	30	31	36	38	32		1
40				3		2	0	0					1

no	Onset	treatment course	Duration of shock	ccf/arrhythmia	Hematology	Liver enzymes	GI system	metabolic	0	duration	start of feeds	type	start of Paladay/DBF (days
1	1	2	3	2	2	3	1	6	1	3	0	0	
2	1	2	3	2	2	2	1	2	0	0	8	1	15
3	1	2	2	2	1	3	1	2	1	2	0	0	
4			0	2	0	3	0	0	0	0	3	1	6
5			0	2	0	3	0	0	0	0	2	2	3
6	1	2	2	2	0	3	0	0	0	0	3	1	4
7			0	2	0	3	0	0	1	1	5	1	10
8	2	3	4	2	1	3	0	4	1	3	0	0	
9			0	2	0	3	0	0	0	0	2	1	5
10	1	2	3	2	0	3	0	0	1	2	5	1	19
11	2	2	3	2	1	3	1	4	1	2	8	1	25
12			0	2	2	3	0	0	0	0	2	1	6
13	1	2	4	2	2	3	0	1	1	2	0	0	
14			0	2	2	3	3	0	1	2	3	1	
15			0	2	2	3	0	0	0	0	4	1	9
16			0	2	2	3	0	0	0	0	3	2	4
17	1	3	1	1	2	3	1	4	1	1	0	0	
18			0	2	2	3	0	4	0	0	3	1	5
19			0	2	2	3	0	0	0	0	2	2	4
20	2	2	3	2	2	3	0	2	1	1	2	1	16
21			0	2	2	3	0	0	0	0	3	2	5
22			0	2	2	3	0	0	0	0	3	2	5
23	1	2	1	2	2	3	1	6	1	1	0	0	
24	1	2	3	2	2	3	1	6	1	1	0	0	
25			0	2	2	3	1	0	0	0	2	1	
26			0	2	1	3	1	0	0	0	3	1	4
27			0	2	2	3	0	0	0	0	3	2	4
28			0	2	2	3	0	0	0	0	3	2	5
29	1	2	1	2	2	3	0	0	0	0	3	1	4
30	1	2	2	1	2	3	0	0	1	2	4	1	
31			0	2	2	3	0	0	1	1	3	1	5
32			0	2	2	3	0	0	0	0	2	2	3
33	1	2	2	2	0	3	0	5	1	2	0	0	
34	1	2	3	1	1	2	1	5	1	3	7	1	28
36	2	2	2	2	2	3	0	3	1	1	0	0	
37	2	2	2	2	2	3	0	4	0	0	0	0	
38			0	2	2	3	0	1	0	0	3	2	4
39	1	2	3	2	2	3	0	4	2	2	0	0	
40	1	3	2	2	2	3	1	5	0	0	0	0	

no	Death	Death/survival with abn ne	Outcome	age at discharge(days)	NE @ Dis/D14	CT	U/S-Cr	MRI	EEG
1	1	1	1			3	3	4	3
2	2	2	2	19	2	3	2	4	3
3	1	1	1			3	3	4	3
4	2	2	2	7	1	3	1	4	3
5	2	2	2	6	1	3	1	4	3
6	2	2	2	6	1	3	3	4	3
7	2	2	2	8	1	3	1	4	3
8	1	1	1			3	3	4	3
9	2	2	2	7	1	3	2	4	3
10	2	2	2	19	1	3	1	4	3
11	2	1	3	25	2	2	2	4	3
12	2	2	2	8	1	3	1	4	3
13	1	1	1			3	3	4	3
14	1	1	1			3	1	4	3
15	2	1	3	15	2	2	1	4	3
16	2	2	2	6	1	3	1	4	3
17	1	1	1			3	3	4	3
18	2	2	2	9	1	3	2	4	3
19	2	2	2	4	1	3	3	4	3
20	2	1	3	16	2	3	2	4	3
21	2	2	2	7	1	3	1	4	3
22	2	2	2	8	1	3	1	4	3
23	1	1	1			3	3	4	3
24	1	1	1			3	3	4	3
25	1	1	*1*			3	3	4	3
26	2	2	2	6	1	3	1	4	3
27	2	2	2	8	1	3	1	3	3
28	2	2	2	8	1	3	1	4	3
29	2	2	2	7	1	3	1	4	3
30	1	1	1			3	3	4	3
31	2	2	2	6	1	3	1	4	3
32	2	2	2	3	1	3	3	4	3
33	1	1	1			3	3	4	3
34	2	1	3	31	1		2	4	3
36	1	1	1			3	3	4	3
37	1	1	1			3	3	4	3
38	2	2	2	5	1	3	1	4	3
39	1	1	1			3	3	4	3
40	1	1	1			3	3	4	3

no	Sl. NO	sex	gest. Age	age in hrs	Pl of Del	age	para	DODel	mod.of del	FHR	MSL	Late decel	Int. part. Compl.
41	A41	1	4	3	2	2	1	7/11/2012	1	4	2	3	1
42	A42	1	3	6	2	2	2	8/8/2012	1	1	2	3	1
43	A43	1	5	4	2	2	1	8/9/2012	1	4	1	3	1
44	A44	1	4	5	2	2	1	8/19/2012	1	4	2	3	1
45	A45	1	2	5	2	2	1	8/21/2012	1	4	2	3	1
46	A46	2	5	6	2	2	1	9/3/2012	1	4	1	3	1
47	A47	1	2	6	2	4	1	9/18/2012	1	4	1	3	1
48	A48	1	3	6	2	2	1	10/2/2012	1	4	2	3	1
49	A49	2	4	2	2	2	1	10/8/2012	1	4	2	2	1
50	A50	2	4	3	2	4	2	10/9/2012	1	4	2	3	1
51	A51	1	4	4	2	3	1	10/9/2012	1	4	2	3	1
52	A52	1	4	6	2	2	1	10/9/2012	3	4	1	3	1
53	A53	2	1	4	1	2	2	10/12/2012	1	1	1	2	1
54	A54	2	3	4	2	3	2	10/12/2012	1	4	2	3	1
55	A55	2	4	4	2	3	2	10/11/2012	1	4	2	2	1
56	A56	1	3	5	1	2	2	10/18/2012	1	2	2	2	1
57	A57	2	5	4	2	2	1	10/22/2012	3	2	1	3	1
58	A58	1	5	3	2	2	1	11/10/2012	1	4	2	3	1
59	A59	1	5	3	2	1	1	10/20/2012	1	4	2	3	1
60	A60	2	5	5	2	1	1	10/29/2012	1	4	2	3	1
61	A61	1	3	6	2	2	1	11/1/2012	1	4	2	3	1
62	A62	1	5	6	2	2	1	11/4/2012	1	4	1	3	1
63	A63	2	4	5	2	2	1	11/7/2012	5	4	1	3	1
64	A64	2	4	6	1	2	1	11/7/2012	5	2	2	2	1
65	A65	1	5	6	2	2	1	11/13/2012	1	4	1	3	1
66	A66	1	5	5	1	2	1	11/11/2012	3	2	1	2	1
67	A67	1	1	5	1	2	1	11/15/2012	5	2	1	2	1
68	A68	1	4	6	1	2	1	11/16/2012	5	2	1	3	1
69	A69	1	4	6	2	2	1	11/16/2012	1	4	2	3	1
70	A70	1	5	5	2	3	2	11/17/2012	1	4	2	3	1
71	A71	2	3	6	2	2	2	11/18/2012	1	4	2	3	1
72	A72	1	5	5	2	2	1	11/19/2012	3	4	1	3	1
73	A73	2	5	4	2	2	1	11/22/2012	1	4	1	3	1
74	A74	1	4	4	2	2	1	11/23/2012	5	4	2	3	1
75	A75	1	5	4	1	3	1	11/25/2012	3	1	2	1	1
76	A76	1	4	4	2	2	2	11/25/2012	1	4	2	3	1
77	A77	1	5	2	2	4	1	11/26/2012	1	4	1	3	1
78	A78	1	5	6	2	2	1	12/1/2012	5	4	2	3	1

no	AN Magsulf	Dur. LaborO	Obstet. Prob	Med. Prob	B. wt	Length	wt/ lt-PI	OFC-cms	apgar 1	apgar 5	apgar 10	resuscitation	duration(min)
41	0	3	1	2	2225	49		33	2	5	6	1	2
42	0	3	1	2	2500	51		34	1	3		1	1
43	0	3	1	2	3000	51		33	3	4	5	1	2
44	0	3	1	2	2500	51		33.5	2	5		1	1
45	0	2	1	2	2670	49		33.5	2	5		1	1
46	0	6	1	2	3000	53		34	2	3		1	1
47	0	3	1	2	2300	51		33				1	1
48	0	3	1	2	2800	51		34.5	2	5		1	1
49	0	2	1	2	2300	52		33	2	5		1	1
50	0	3	1	2	2030	45		32	2	5		1	1
51	0	3	1	2	2900	50		34.5	2			1	1
52	0	3	1	2	2750	51		33	2	6		1	1
53	0	3	2	2	2000	47		33	2	2	4	2	2
54	0	1	1	2	3000	52		33.5	2			1	2
55	0	3	1	2	3700	54		35	2	3		3	2
56	0	3	1	2	3125	51		34	3	5	6	3	1
57	0	1	1	2	3000	50		34	2	5	5	3	2
58	0	3	1	2	3050	49		33.5	2	3	5	3	3
59	0	2	1	2	3010	51		34	2	3	5	1	2
60	0	3	1	2	2600	49		33.5	2	5		1	1
61	0	2	1	2	2600	50		33	2	5		3	2
62	0	2	1	2	3200	49		33	2			1	1
63	0	2	1	2	2860	50		33	2	5		1	1
64	0	2	1	2	2580	49		33.5	2	7		3	1
65	0	3	1	2	2793	50		34	3			2	2
66	0	3	1	2	2500	54		30	2	4	6	3	2
67	0	3	2	2	2100	45.5		32	3	5	6	3	1
68	0	2	1	2	2800	52		34	3	4	6	2	2
69	0	2	1	2	2500	59		34	2	4		1	2
70	0	3	1	2	3000	50		36	2	4		2	2
71	0	3	1	2	2370	49		33.5				1	1
72	0	3	1	2	3250	50		34	2	4		3	2
73	0	3	1	2	3200	54		34	1	5	5	1	1
74	0	3	1	1	2820	52		33	2	5		1	1
75	0	2	1	2	3125	55		35	2	4	4	3	2
76	0	1	1	1	2960	52		33.5	2	4		1	1
77	0	2	1	2	2680	52		34	2	4		1	2
78	0	3	1	2	3250	51		35	2			1	1

no	seizures < 6hrs	HIE	GROUP(drug)	Sr Mg preinj	post inj	23 hrs	26hrs	47hrs	50hrs	71hrs	Onset of seizure within 24 hrs	course of seizures	HIE-D!
41	1	2	1	0.94	2.4	2.2		1.9			1	2	2
42	1	2	1	0.9	1.8	0.8	1.6	1.8	2.6	1.8	1	2	2
43	2	2	1	1.1	2.4	1.1	1.8	1.8	1.9	1.7	2	1	2
44	1	2	0	1.2	0.98	0.9	1	0.7	1.1	0.8	1	2	2
45	1	2	0	1.2	1.1	0.9		0.86	0.94	0.5	1	2	2
46	1	2	1	1	2.3	1.3	1.7	1.8	2	1.8	1	3	2
47	1	2	1	0.8	1.3	1.2	1.9	1.8	2.2	1.9	1	3	2
48	1	2	0	0.4	0.5	1.2	1.4	0.8	0.5	0.5	1	2	2
49	1	2	0	1.1	1.2	1.2		1.1	1	1.2	1	2	2
50	1	2	0	0.7	1.2	0.98	0.94	1.1	0.96	0.64	1	3	2
51	1	2	1	0.7	1.9	1.3	2.2	2.8		2	1	3	2
52	1	2	1	0.9	2	1.5	2.1	2.3	2.8	2.1	1	3	2
53	1	3	1	1.1	2.9	1.7		2.2	2.7	1.6	1	2	2
54	1	2	0	1.1	0.89	0.98		1.1	0.69	0.96	1	2	2
55	2	3	1	1.1	2.5						1	2	3
56	1	2	1	0.98		1.6	2.5	1.8	2.9	1.9	1	2	2
57	2	3	0	0.76	0.96	0.78	0.74	0.76		0.8	2	2	3
58	1	2	0	1	0.69	0.7	0.68	0.72	0.84	0.64	1	3	2
59	2	3	0	1.1		1	1	0.9		1.1	2	1	3
60	1	2	1	1.1	2.6	1.8		1.5	2.6		1	2	2
61	1	2	0	0.6	1.1	0.6	0.6	0.8		1.1	1	2	2
62	1	2	1	0.9	2.1	1.6	2	1.8	2.6		1	2	2
63	2	2	1	0.9	1.9	1.6	2	1.3		3.1	2	1	2
64	1	2	0	1		1.1		1.1		1.2	1	2	2
65	2	3	0	1.1	0.96	1.2					2	1	3
66	2	3	1	1.9	3	2.4	2.9	2.5	2.5	2.3	2	1	2
67	1	2	0	1	0.93	0.9	1.1	1			1	2	2
68	2	2	1	1.1	2.5	1.7	2.4	2.4			1	2	3
69	2	2	0	0.92	1.1	0.94	1	1.2	1.1	1	1	2	2
70	2	3	1	1	1.9	1.8					2	1	3
71	1	2	0	0.89		0.92	0.7	1.1	0.95	1.1	1	3	2
72	2	3	1	1.1	1.7						2	1	3
73	1	2	0	1.1		0.98		1.1	0.99	0.98	1	2	2
74	2	2	1	0.98	3	1.2	1.9	1.7	1.9		2	1	2
75	1	3	0	1	1.1	0.7	0.6	0.7	0.7	0.8	1	2	3
76	1	2	0	1.2	1.2	1.1	1	0.9	0.94		1	2	2
77	1	2	1	1	2.2	1.3	2.5	1.6		2.4	1	2	2
78	1	2	1	1.2	2	1.6	2.5	1.7	2.3	1.8	1	2	2

no	HIE D2	HIE-D3	HIE D4 onwards	Resp support @ Adm	MV after 24hrs-day4	days of MV	MAP bef Inj 0hrs	MAP aft Inj	bef inj 24hrs	aft inj 26hrs	bef inj 48hrs	aft inj 50hrs	Shock
41	2	1	0	2	2		36	42	40	44	42	46	1
42	2	2	3	3		8	43	42	42	42	43	42	1
43	3	3	3	2	1	4	44	78	56	58	54	52	1
44	2	2	3	3		4	45	44	42	43	42	56	1
45	2	1	1	2	2		39	41	43	46	45	46	2
46	2	2	2	2	1	4	39	54	34	50	40	44	1
47	2	2	0	2	2		31	37	34	44	44	45	1
48	2	2	2	1	2		42	40	42	42	40	33	1
49	2	0	0	1	2		44	44	45	42	44	40	2
50	2	3	3	2	1	4	44	40	36	39	36	39	1
51	2	2	2	1	2		55	53	45	42	45	42	2
52	2	3	3	2	1	3	42	44	40	42	26	27	1
53	2	2	3	3		7	42	43	44	44	29	26	1
54	2	2	0	2	2		42	39	44	44	44	42	2
55	3			3		2	30	33	27	29			1
56	2	0	0	1	2		44	45	44	45	42	44	2
57	3	3	3	3		7	36	40	52	50	51	50	1
58	2	2	2	2	2		44	43	46	42	47	46	2
59	3		3	3		4	32	46	40	47	32	36	1
60	2	2	2	2	2		33	40	45	46	44	48	1
61	2	2	2	2	1	4	51	55	42	41	38	40	1
62	3	3	3	2	1	3	40	40	33	53	36	38	1
63	2	0	0	2	2		35	39	45	48	44	46	1
64	2	2	0	1	2		44	46	40	39	42	44	2
65	3			3		2	40	40	32	30			1
66	2	0	0	3		2	42	40	40	45	40	42	2
67				3			42	44	39	40			2
68	3			3		3	42	44	40	42			1
69	0	0	0	1	2		42	46	44	42	40	45	2
70	3			3		3	36	34	30	32			1
71	2	3	3	2	1	8	42	46	32	36	44	40	1
72				3		2	42	36					1
73	2	0	0	1	2		54	52	52	52	52	51	2
74	2	2	2	2	2		44	41	45	43	44	43	2
75	3	3		3		3	36	40	44	44	36		1
76	2	2	2	2	2		35	34	40	46	44	43	1
77	2	2	2	2	2		49	46	44	42	40	44	2
78	2	2	0	2	2		46	44	35	44	45	46	1

no	Onset	treatment course	Duration of shock	ccf/arrhythmia	Hematology	Liver enzymes	GI system	metabolic	0	duration	start of feeds	type	start of Paladay/DBF (days
41	1	2	2	2	2	3	0	0	0	0	3	2	4
42	1	2	2	1	2	3	0	1	0	0	0	0	
43	1	2	2	1	2	3	0	4	1	2	0	0	
44	2	2	4	2	2	3	0	4	1	3	0	0	
45			0	2	2	3	0	2	0	0	3	2	4
46	1	2	2	2	2	3	0	2	0	0	7	1	12
47	1	2	2	2	2	3	0	0	0	0	3	1	5
48	2	2	3	2	1	3	0	5	1	2	3	1	14
49			0	2	2	3	0	0	0	0	3	3	3
50	1	3	4	1	1	3	1	6	1	2	0	0	
51			0	2	2	3	0	5	1	2	5	1	9
52	2	2	3	2	2	3	0	6	1	2	0	0	
53	1	2	4	2	2	3	0	6	0	0	0	0	
54			0	2	2	3	0	0	0	0	3	1	4
55	1	3	2	1	2	3	1	6	1	2	0	0	
56			0	2	2	3	0	0	0	0	3	2	3
57	1	2	2	2	2	3	1	5	1	3	0	0	
58			0	2	2	3	0	0	0	0	3	1	6
59	1	3	4	2	2	3	0	2	0	0	0	0	
60	1	2	2	2	2	3	0	0	0	0	3	1	5
61	1	2	3	2	2	3	0	0	0	0	6	1	8
62	1	2	4	2	2	3	0	0	1	2	0	0	
63	1	2	2	2	2	3	0	0	0	0	4	1	5
64			0	2	2	3	0	0	0	0	3	1	5
65	1	2	2	2	2	3	1	6	1	1	0	0	
66			0	2	2	3	0	0	0	0	4	1	5
67			0	2	2	3	1	0	0	2	0	0	
68	2	2	2	2	2	3	0	0	1	1	0	0	
69	2		0	2	2	3	0	0	0	0	2	3	3
70	1	2	3	2	1	3	0	5	1	2		0	
71	2	2	2	2	2	3	1	5	1	3	8	1	22
72	1	2	2	2	2	3	1	6	1	1	0	0	
73			0	2	2	3	0	0	0	0	2	1	4
74			0	2	2	3	0	6	0	0	3	1	8
75	1	2	3	1	2	3	0	6	1	2	0	0	
76	1	2	2	2	2	3	0	6	0	0	4	1	6
77			0	2	2	3	0	0	0	0	3	1	5
78	2	2	2	2	2	3	1	0	0	0	3	1	5

no	Death	Death/survival with abn ne	Outcome	age at discharge(days)	NE @ Dis/D14	CT	U/S-Cr	MRI	EEG
41	2	2	2	6	1	3	1	4	3
42	2	1	4	8	2	2	2	4	3
43	1	1	1			3	3	4	3
44	1	1	1			3	3	4	3
45	2	2	2	5	1	3	1	4	3
46	2	1	3	14	2	3	2	4	3
47	2	2	2	7	1	3	2	4	3
48	2	1	3	10	2	3	2	4	3
49	2	2	2	3	1	3	1	4	3
50	1	1	1			3	3	4	3
51	2	1	3	10	1	3	2	4	3
52	1	1	1			3	3	4	3
53	1	1	1			3	3	4	3
54	2	2	2	6	1	3	2	4	3
55	1	1	1			3	3	4	3
56	2	1	3	7	1	3	1	4	3
57	1	1	1			3	3	4	3
58	2	2	2	7	1	3	3	4	3
59	1	1	1			3	3	4	3
60	2	2	2	6	1	3	1	4	3
61	2	2	2	8	1	3	1	4	3
62	1	1	1			3	3	4	3
63	2	2	2	6	1	3	2	4	3
64	2	2	2	6	1	3	1	4	3
65	1	1	1			3	3	4	3
66	2	2	2	6	1	3	1	4	3
67	1	1	1			3	3	4	3
68	1	1	1			3	3	4	3
69	2	2	2	4	1	3	1	4	3
70	1	1	1			3	3	4	3
71	2	1	3	30	2	3	2	4	3
72	1	1	1			3	3	4	3
73	2	2	2	6	1	3	1	4	3
74	2	2	2	9	1	3	2	4	3
75	1	1	1			3	3	4	3
76	2	2	2	7	1	3	1	4	3
77	2	2	2	8	1	3	1	4	3
78	2	2	2	8	1	3	2	4	3

no	Sl. NO	sex	gest. Age	age in hrs	Pl of Del	age	para	DODel	mod.of del	FHR	MSL	Late decel	Int. part. Compl.
79	A79	1	2	5	2	2	2	11/27/2012	1	4	1	3	1
80	A80	1	5	3	2	2	1	12/1/2012	3	2	2	2	1
81	A81	1	2	5	2	1	1	12/7/2012	3	4	2	3	1
82	A82	2	5	5	2	2	1	12/10/2012	1	4	1	3	1
83	A83	1	5	5	2	2	1	12/10/2012	1	4	1	3	1
84	A84	1	5	6	2	3	2	12/10/2012	1	4	2	3	1
85	A85	1	5	4	2	2	1	11/17/2012	1	4	2	3	1
86	A86	1	2	4	2	2	1	12/17/2012	1	4	2	3	1
87	A87	2	2	4	2	2	1	12/19/2012	1	4	1	3	1
88	A88	1	4	5	2	2	1	12/19/2012	1	4	1	3	1
89	A89	1	2	4	2	3	2	12/20/2012	1	4	1	3	1
90	A90	1	3	5	1	2	1	12/24/2012	2	2	2	2	1
91	A91	1	5	5	2	3	2	12/27/2012	1	4	2	3	1
92	A92	2	5	4	2	2	1	12/30/2012	1	4	1	3	1
93	A93	2	4	5	1	3	1	12/31/2012	5	2	2	2	1
94	A94	1	3	3	2	2	1	1/3/2013	1	4	1	3	1
95	A95	1	5	4	2	2	1	1/4/2013	1	4	2	3	1
96	A96	2	3	3	2	2	1	1/9/2013	1	4	1	3	1
97	A97	2	5	6	2	3	2	1/3/2013	1	4	2	3	1
98	A98	1	3	5	2	2	1	1/12/2013	1	4	1	3	1
99	A99	2	2	3	2	3	1	1/12/2013	1	4	2	3	1
101	A101	2	5	5	2	2	1	1/14/2013	1	4	2	3	1
102	A102	2	4	3	1	2	1	1/15/2013	5		1	2	1
103	A103	2	4	6	2	2	1	1/14/2013	1	4	2	3	1
104	A104	1	5	5	1	2	1	1/15/2013	3	2	1	2	5
105	A105	1	4	5	2	2	1	1/18/2013	1	4	2	3	1
106	A106	1	5	5	1	5	2	1/27/2013	3	2	1	2	1
107	A107	1	3	4	2	2	1	1/27/2013	1	4	1	3	1
108	A108	1	3	5	2	2	1	1/25/2013	1	4	1	3	1
109	A109	2	4	4	1	3	1	1/25/2013	3	2	1	2	1
110	A110	1	3	5	1	3	1	1/29/2013	1	2	2	2	1
111	A111	2	2	3	1	4	2	1/29/2013	3	2	2	1	1
112	A112	1	3	5	1	2	1	1/31/2013	1	2	2	2	5
113	A113	2	5	5	2	2	1	2/19/2013	1	4	1	3	1
115	A115	1	1	2	1	3	1	2/19/2013	3	2	2	2	1
116	A116	1	1	2	1	3	1	2/19/2013	1	2	2	2	1
117	A117	2	3	5	2	2	1	2/20/2013	1	4	1	3	1
118	A118	2	2	2	1	2	1	2/22/2013	5	2	1	2	1
119	A119	2	4	6	1	2	2	2/22/2013	3	2	1	2	1

no	AN Magsulf	Dur. LaborO	Obstet. Prob	Med. Prob	B. wt	Length	wt/ lt-PI	OFC-cms	apgar 1	apgar 5	apgar 10	resuscitation	duration(min)
79	0	1	1	2	3500	51		34	2	5		1	1
80	0	3	1	2	2730	51		34	0	3	5	1	1
81	0	5	1	2	3300	51.5		3	2	5	5	1	1
82	0	2	1	2	3300	51		35	2	6		1	1
83	0	3	1	2	2500	53		34	2	4		1	1
84	0	3	1	2	3000	50		35	2	5		1	1
85	0	3	1	2	3150	51		34	2	6		1	1
86	0	2	1	2	2250	49		32	2	5		1	1
87	0	3	1	2	2850	49		33	2	4		1	2
88	0	5	1	2	3080	50		35	2			1	1
89	0	2	1	2	2800	51		35	2	5		1	2
90	0	6	1	2	2750	52		34	2	3	5	3	2
91	0	2	1	2	3600	52		36	2	6		1	1
92	0	3	1	2	2850	51		33.5				1	1
93	0	3	1	2	3200	49		36	2	5	6	3	1
94	0	3	1	2	2250	48		32				1	1
95	0	2	1	2	3000	53		35				1	1
96	0	3	1	2	2500	53		34				1	1
97	0	1	1	2	3000	51		34				1	1
98	0	2	1	2	2488	49		33	2			1	1
99	0	2	1	2	3070	50		35	2	6		1	1
101	0	3	1	8	2830	51		35.5	2	5		3	1
102	0	3	1	8	3040	51		33	2	5	6	1	1
103	0	3	1	8	2420	49		33	2	5		3	2
104	0	3	1	8	2665	52		35	2	5	7	2	1
105	0	5	1	8	3250	49		34	2	4	5	1	1
106	0	3	1	2	3700	54		35	2	5	7	1	1
107	0	2	1	8	3000	53		35	2	5		1	3
108	0	5	1	8	3140	51		34				1	1
109	0	3	1	8	2280	49		32	1	3	5	3	1
110	0	3	1	8	3000	49		33	2	5	7	3	1
111	0	3	1	8	3250	51		32	1	4	6	3	1
112	0	4	1	8	2200	49		31.5	2	5	6	2	1
113	0	3	1	8	2480	49		33	2			1	1
115	0	3	4	8	2150	47		32	2	6		1	1
116	0	3	4	8	2320	49		33	2	6	7	1	1
117	0	3	4	8	3100	51		34				1	1
118	0	3	1	8	2400	49		33	2	5	5	3	1
119	0	3	2	8	1960	48		32	2	5	6	1	1

no	seizures < 6hrs	HIE	GROUP(drug)	Sr Mg preinj	post inj	23 hrs	26hrs	47hrs	50hrs	71hrs	Onset of seizure within 24 hrs	course of seizures	HIE-D!
79	1	2	1	0.9	1.7	1.5		1.6	2.1	2.1	1	2	2
80	2	2	0	1.2	0.82	1.1		1.2	0.96		2	1	2
81	1	2	0	0.9	1.2	0.8		0.7	0.6	0.8	1	3	2
82	1	2	1	1.1	1.3	1.5		2.2	2.3	2.2	1	2	2
83	2	2	1	1.1	1.7	1.7		1.4		1.9	2	1	2
84	2	2	0	1.1	1.2	1	1.1	0.8		1.2	1	3	2
85	2	2	1	0.9	3.1	1.7	2.7	1.2	2.1	2.2	2	1	2
86	2	2	0	0.5	1	0.7	0.7			1	2	1	2
87	2	3	0	0.9							2	1	3
88	1	2	1	1.1	2	1.6	3.2	1.6	3.2	1.6	1	3	2
89	2	3	0	0.8	0.9						2	1	3
90	2	2	1	1.2	3.2	2.8	3.2	2.5	3		2	1	3
91	1	2	0	0.7	0.7	1	0.6	0.6	1.1	0.9	1	3	2
92	1	2	1	1.2	2.9	1.9	2.4	1.5	2.5		1	3	2
93	1	2	0	0.7		0.8	0.8	1.1	1.2	0.9	1	2	2
94	2	2	0	1.1	1.1	1.2	0.9	1.1	1.2		2	1	2
95	1	2	1	1.2	2.2	1.8	2.3	2		3	1	2	2
96	1	2	1	0.9	2.1		3	1.7	2.3	1.7	1	3	2
97	1	2	0	0.9	1.1	1.2	1	0.8	1.2	1.2	1	2	3
98	1	2	1	1.2	2.6	1.8					1	2	2
99	1	2	0	1.1	0.89	1.1	1	1.2	1.2	1.1	1	2	2
101	1	2	1	1.1	3	1.3	2.3	1.2	2	1.2	1	2	2
102	1	2	1	0.8	1.5	0.7	1.8	1		1.5	1	2	2
103	1	2	0	1.1		0.9	0.86	1.2	1.1	1.1	1	2	2
104	2	2	0	1.1		1.03	0.94	0.9	0.7	1	1	2	2
105	1	2	0	1.1	0.86	0.87	0.78	0.65	0.98	0.78	1	2	2
106	1	2	1	1.1	2.4	1.2	2.3	1.3	3	2.14	1	2	2
107	1	2	1	1.1	2.2	2	2.97	1.64	2.34	2	1	3	3
108	1	2	1	1.1	2	1.6	2.35	1.6		1.31	1	3	3
109	2	2	0	1	1.2	0.78	0.82	1.2	1.1	1	2	1	2
110	2	2	0	1.07	1.04	0.75	0.82	1.1	1.15	1	1	2	2
111	2	2	0	0.53	0.86	1		0.78	0.78		2	1	2
112	1	2	1	0.8	1.6	1.5		2.6			1	2	3
113	1	2	1	0.53	1.6	1.55					1	2	3
115	1	2	0	0.65	0.45	0.49	0.61	0.74	0.53	0.65	1	2	2
116	1	2	0	0.57	0.4	0.61	0.61	0.49	0.61	0.4	1	2	2
117	1	2	1	0.61	2.3	1.7		2.06	1.52	1.45	1	3	2
118	1	2	1	1.06	2	1.5	2.26	1.45	2.2	1.5	1	2	2
119	1	2	0	1.03	1.05	0.9		1.03	0.94	0.94	1	2	2

no	HIE D2	HIE-D3	HIE D4 onwards	Resp support @ Adm	MV after 24hrs-day4	days of MV	MAP bef Inj 0hrs	MAP aft Inj	bef inj 24hrs	aft inj 26hrs	bef inj 48hrs	aft inj 50hrs	Shock
79	2	3	3	2	1	6	32	40	53	52	44	48	1
80	2	0	0	1	2		42	42	44	43	42	43	2
81	2	2	3	2	1	1	50	52	42	40	48	44	1
82	2	2	2	2	2		35	39	35	39	40	44	1
83	2	2	2	2	2		48	46	47	50	46	48	2
84	3	3	2	3		3	46	33	54	56	4	46	1
85	2	0	0	2	2		44	42	44	42	40	42	2
86	2	2	0	2	2		42	42	42	40	46	52	2
87				3		1	32	0					1
88	2	2	2	2	2		40	42	52	50	49	50	2
89	3			3		2	34	36					1
90	3	3	3	3		3	38	45	52	54	28	28	1
91	3	3	2	2	1	2	42	30	39	42	44	46	1
92	2	3	3	2	1	2	42	44	58	52	56	54	1
93	2	2	0	2	2		44	56	44	44	42	42	2
94	2	0	0	2	2		44	44	42	40	44	42	1
95	2	3	3	2	1	3	35	44	54	56	55	54	1
96	2	2	2	1	2		34	40	38	40	41	42	1
97	3	3	3	3		8	44	42	42	44	40	39	1
98	3			2	1	2	40	41	65	57			2
99	2	2	0	1	2		42	44	44	40	42	40	2
101	2	2	2	2	1	3	46	46	48	42	44	45	1
102	2	2	0	2	2		42	46	45	44	46	48	2
103	2	3	3	2	1	8	41	44	40	42	37	38	1
104	2	2	3	2	1	2	34	37	46	44	46	48	1
105	2	1	0	2	2		37	42	44	46	42	44	1
106	2	2	3	3		5	44	46	44	42	40	44	1
107	3	3	3	3		5	37	39	40	38	42	44	2
108	3	2	2	3		3	35	43	44	42	44	46	1
109	2	2	0	3		2	44	41	48	44	46	51	2
110	2	2	0	3		1	54	55	53	53	52	54	2
111	2	2		2	2		35	55	55	52	38	36	1
112	3			3		3	41	41	40	36			1
113	3			3		3	50	52	33	35	0		1
115	2	2	0	3		1	38	39	40	36	42	40	2
116	2	2	0	2	2		37	36	39	44	40	42	2
117	2	3	3	3		5	31	38	38	42	53	44	2
118	2	2	2	3		8	36	42	42	40	39	40	1
119	2	2	2	3		1	44	42	42	46	44	46	2

no	Onset	treatment course	Duration of shock	ccf/arrhythmia	Hematology	Liver enzymes	GI system	metabolic	0	duration	start of feeds	type	start of Paladay/DBF (days
79	1	2	4	1	2	3	1	6	0	0	0	0	
80			0	2	2	3	0	0	0	0	2	2	4
81	2	2	2	2	1	3	1	3	1	2	0	0	
82	1	1	1	2	1	3	0	5	0	0	3	1	8
83			0	2	2	3	3	5	0	0	6	1	8
84	2	2	2	2	2	3	0	6	0	0	6	1	8
85			0	2	2	3	0	0	0	0	1	1	3
86			0	2	2	3	0	0	0	0	2	1	3
87	1	3	1	2	2	3	1	6	0	0	0	0	
88		0	0	2	2	3	0	0	0	0	2	1	
89	1	2	2	2	2	3	0	6	1	1	0	0	
90	1	2	2	2	1	3	1	6	0	0	0	0	
91	1	2	2	2	2	3	1	6	1	3	4	1	9
92	2	2	3	2	2	3	1	7	2	1	0	0	
93		0	0	2	2	3	0	0	0	0	2	1	6
94		0	0	2	2	3	0	0	0	0	2	2	3
95	1	2	2	2	2	3	0	0	0	0	3	1	0
96	1	2	3	2	2	3	0	0	0	0	4	1	10
97	1	2	3	2	2	3	0	7	1	1	3	1	18
98			0	2	2	3	0	6	1	1	0	0	
99			0	2	2	3	0	0	0	0	2	1	6
101	1	2	2	2	2	3	0	0	0	0	5	1	11
102			0	2	2	3	0	0	0	0	2	2	4
103	2	2	4	1	2	3	1	6	1	3	1	0	
104	1	2	3	2	2	3	2	4	1	2	0	0	
105	1	2	1	2	2	3	0	0	0	0	2	2	3
106	3	2	3	2	2	3	0	4	1	3	4	1	14
107			2	2	2	3	0	6	1	2	5	1	
108	1	2	2	2	1	3	0	6	0	0	5	1	8
109			0	1	2	3	0	6	0	0	3	1	6
110			0	2	2	3	0	0	0	0	2	1	5
111	2	2	3	2	2	3	1	0	0	0	0	0	
112	1	2	3	2	2	3	1	6	0	0	0	0	
113	2	3	2	2	2	3	0	6	1	1	0	0	
115			0	2	2	3	0	0	0	0	3	2	4
116			0	2	2	3	0	1	0	0	4	2	4
117			0	2	2	3	0	0	0	0	7	1	12
118	1	2	4	2	1	3	0	0	1	3	0	0	
119			0	2	2	3	0	1	0	0	4	1	7

no	Death	Death/survival with abn ne	Outcome	age at discharge(days)	NE @ Dis/D14	CT	U/S-Cr	MRI	EEG
79	1	1	1			2	3	4	3
80	2	2	2	4	1	3	2	4	3
81	1	1	1			3	3	4	3
82	2	2	2	9	1	3	2	4	3
83	2	2	2	22	1	3	1	4	3
84	2	1	3	10	2	3	2	4	3
85	2	2	2	5	2	3	3	4	3
86	2	2	2	6	1	3	2	4	3
87	1	1	1			3	3	4	3
88	1	1	1			3	2	4	3
89	1	1	1			3	3	4	3
90	1	1	1			3	3	4	3
91	2	2	2	14	1	3	2	4	3
92	1	1	1			3	3	4	3
93	2	1	3	10	2	2	1	4	3
94	2	2	2	4	1	3	1	4	3
95	1	1	1			3	3	4	3
96	2	2	2	14	1	3	2	4	3
97	2	1	3	21	2	2	2	4	3
98	1	1	1			3	3	4	3
99	2	2	2	7	1	3	1	4	3
101	2	1	3	14	2	3	2	4	3
102	2	2	2	6	1	3	1	4	3
103	1	1	1			3	3	4	3
104	1	1	1			3	3	4	3
105	2	2	2	6	1	3	1	4	3
106	2	2	2	14	1	3	2	4	3
107	1	1	1			3	3	4	3
108	2	1	3	12	2	3	1	3	3
109	2	2	2	7	1	3	1	4	3
110	2	2	2	8	1	3	2	4	3
111	1	1	1			3	3	4	3
112	1	1	1			3	3	4	3
113	1	1	1			3	3	4	3
115	2	2	2	9	1	3	1	4	3
116	2	2	2	9	1	3	1	4	3
117	2	2	2	14	1	3	1	4	3
118	1	1	1			2	3	4	3
119	2	2	2	14	1	3	1	4	